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BRITISH
HEART
JOURNAL

Editorial

British Heart Journal: content . . .

Readers will already have noticed the altered format of the *British Heart Journal,* with larger pages (A4 size) and subtle redesign of the front cover and page structure. These are forward looking ideas, which are discussed in more detail in the companion editorial below. Rest assured that, despite the change in packaging, the quality of the ingredients and the flavour of the *British Heart Journal* remain the same. The journal will continue to publish editorials, original studies, and case reports—chosen by peer review and by final discussion in the editorial office. There will be no short measure: the journal will continue to publish the same amount of text.

Steps to improve the quality of the content continue. The journal was an early partner in the change to the Vancouver style, which standardised several elements, especially references.[1] In 1988 the *British Heart Journal* published guidelines to promote the use of appropriate statistical design and analysis—emphasising the usefulness of confidence intervals.[2] In harmony with companion journals published by the *British Medical Journal* group, several other developments are being implemented.

Our preference for literate abstracts continues. We aim to entice the reader to study the full article and not to rely on a few isolated numbers within the abstract, which may be misleading. The use of confidence intervals may partly overcome this. More specifically, for clinical trials, we aim to publish structured abstracts provided by the authors as part and parcel of the article. The structured abstract has been well defined by Lock, and when appropriate should be used to indicate the objective, design, setting, participants, interventions, measurements and results, and key conclusions.[3]

Readers should already have noted an improvement in the reproduction of black and white and colour illustrations. We are making greater use of computerised scanning techniques to prevent the degradation of what might sometimes be fairly faint images in the original.

Like other major journals, the *British Heart Journal* wants to publish the full story and not instalments. "Salami" publication, in which different elements of the same study are scattered in different places, clogs the journals, and prevents the reader from getting a comprehensive view of a subject in a single article.[4] The equally disparaging term "meat extender" is applied to those articles where a little bit extra—usually a few cases—is added to an earlier report. It is often not clear which cases have been reported before and the body of knowledge is distorted by both approaches.

The *British Heart Journal* wants the developments reported on its pages to be seen first by the readers, and not disseminated by pre-emptive publication in the lay press, through extracts published in commercially orientated articles, or the like.

And what of new content? There will be more reviews of books chosen because they are unlikely to have received attention in the weekly medical press and because they are of specific cardiological interest and have that extra flavour which appeals to our readers. Also the journal has assembled a series of historical photographs from various sources, including the collections of the late John Hay of Liverpool and of Sir Thomas Lewis; these will appear with legends to remind us of the past and how and who thought things out.

DENNIS M KRIKLER

Editor,
British Heart Journal

. . . and style

In 1989 the *British Heart Journal* celebrated its first 50 years. This milestone and the start of a fresh decade make it a good time for the journal to appear in a new suit—one that is larger and allows for a more flexible layout and better presentation of tables and illustrations.

The cover

The journal has never been a slave to fashion. The original familiar crimson jacket that it wore for almost a third of a century was shed only in 1970. As the editor, Kenneth Shirley Smith, wrote at the time, the "stylish modern" glossy white front cover with maroon border around the contents was designed "with the priority of instant recognition and immediate presentation of contents" firmly in mind.[5] The minutes of the Editorial Committee meeting held in 1969 to discuss plans for the redesign hopefully record that "A 'new look' cover would also encourage more of the younger cardiologists to send their papers to the *British Heart Journal*; at present its rather staid appearance perhaps discourages the younger research workers". The impact of the 1970 cover on the Young Turks of cardiology is difficult to judge but there is no doubt it did establish a brand image, which the journal was keen to retain with the new larger 1990 format. The new design retains the familiar glossy white cover with a maroon frame for the list of contents; this should ensure that the *British Heart Journal* continues to be instantly recognisable.

Layout

The 1970 design for the typography and page layout served the journal well. But inevitably the purity of the original design was corrupted by the month to month expediencies of accommodating changing contents and a considerable growth in the number of figures and tables. The format was serviceable but dated and the *British Heart Journal* was beginning to look its age, with a profile somewhat blurred in middle age.

These aesthetic considerations alone would soon have prompted a review of the journal's design. But for most of the specialist journals published by the *BMJ* group there were also economic and practical gains to be made out of changing to a larger page. The move to a larger standard metric paper—A4—will lead to economies in production for all nine journals in the *BMJ* stable that are abandoning crown quarto paper, which is now a non-standard size and hence expensive.

The change to a larger page gave the ideal opportunity of bringing a fresh eye—that of Ray Fishwick—to the variegated styles of all the special journals in the *BMJ* stable. Up till now most of the special journals have followed their own inclinations and this has meant that the compositors at the printers have had to know about and recall the time consuming typographical idiosyncrasies of all the *BMJ* journals that they set. Now, production will be streamlined by the unified design.

In formulating a basic design for the group the designer was careful to consult with each of the journals before settling for an approach that can cope with their individual requirements and presents an up to date corporate image for the whole stable.

But for readers and authors the main advantage of the new five column design lies in its greater flexibility for presenting tables and illustrations. A redesign is as unsettling as having decorators in—but once the smell of paint has gone, readers and authors should feel as comfortable in their new more spacious surroundings as they were in the old ones.

JANE DAWSON

Technical Editor,
British Heart Journal

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Br Heart J 1990;63:3-4

Editorial

Electrophysiological basis for the use of adenosine in the diagnosis and treatment of cardiac arrhythmias

The nucleoside adenosine has increasingly been recognised to be useful in the treatment and diagnosis of cardiac arrhythmias.[1-5] The most recent articles of Rankin *et al*[6] and Till *et al*[7] confirm this and provide further evidence of the usefulness and applicability of giving intravenous boluses of adenosine as a therapeutic and diagnostic tool in the short term management of supraventricular arrhythmias.

An understanding of the cellular electrophysiological effects of adenosine was vital in the development of the clinical use of this nucleoside.[8] The potential for developing additional clinical uses for adenosine or related compounds (that is agonists and antagonists) rests on further delineation of the cellular and molecular mechanisms of their action.

Our object is to describe the current knowledge of the cellular electrophysiological actions of adenosine and to provide well established examples in which such knowledge has led to the successful use of this nucleoside in the management of cardiac arrhythmias.

Basis of action of adenosine

Adenosine is an endogenous nucleoside whose production is increased in response to stimuli such as hypoxia and ischaemia.[8] In addition to its coronary vasodilatory properties, adenosine has considerable electrophysiological effects on the specialised tissues of the heart—that is the sinoatrial and atrioventricular nodes and working myocardium.[8] Adenosine induced depression of the pacemaker activity of the sinoatrial node and of atrioventricular nodal transmission is responsible for the negative chronotropic (bradycardia) and dromotropic (atrioventricular block) effects caused by the nucleoside. Thus adenosine regulates atrial and ventricular rates independently of each other. In addition to these effects on the specialised tissues, adenosine produces a concentration-dependent shortening of the action potential and hyperpolarisation in the atrial myocardium—effects that are accompanied by a negative inotropic response.[8] On the other hand, in the absence of catecholamine stimulation, adenosine causes no discernible electrophysiological or inotropic effect in ventricular myocardium.[8 9] So adenosine has no effect unless the adenylyl cyclase-cAMP system is first stimulated. However, under conditions of enhanced adenylyl cyclase activity (that is raised concentrations of cAMP), the electrophysiological (including triggered activity) and positive inotropic effects of β adrenergic stimulation are antagonised by adenosine.[8 9]

The cellular basis for adenosine's effects in supraventricular tissues is mainly the activation of a specific potassium-outward current ($I_{KACh,Ado}$)—that is the so-called acetylcholine regulated potassium channels.[10 11] Other mechanisms of action of adenosine include inhibition of the catecholamine stimulated calcium inward current (I_{Ca}) and in sinoatrial node cells attenuation of the pacemaker current (I_F) stimulated by isoprenaline.[12 13] In contrast, the figure shows that the acetylcholine regulated potassium channels are not present in ventricular myocytes; the electrophysiological actions of adenosine in these cells are mainly caused by the attenuation of catecholamine stimulated I_{Ca} and catecholamine induced transient inward currents (I_{Ti}), which is responsible for the delayed afterpotentials that often lead to trigger activity.[14 15] Pacemaker activity arising from Purkinje fibres, stimulated by catecholamines, can also be depressed by adenosine.[16]

Clinical actions of adenosine

These electrophysiological properties of adenosine, for the most part, form the basis for its clinical antiarrhythmic actions. Adenosine has proved to be effective (>90%) in terminating supraventricular tachycardia in which the atrioventricular node forms one of the limbs of the reentrant circuit, such as atrioventricular reciprocating tachycardia and atrioventricular nodal reentry.[1] By transiently interrupting impulse propagation through the atrioventricular node, adenosine effectively terminates these types of supraventricular arrhythmias. Some accessory pathways with decremental conduction properties have also been shown to be sensitive to adenosine,[17] which could explain the adenosine induced termination of long RP′ tachycardia in the retrograde limb of the reentrant circuit reported by Till *et al.*[7] Transient atrioventricular block caused by adenosine has also been shown to be useful in unmasking atrial rhythms (for example, atrial tachycardia and flutter) that are otherwise concealed by the ventricular depolarisations.[1 4] In addition, in atrial tissue, hyperpolarisation (caused by an increase in $I_{KACh,Ado}$) caused by adenosine may stabilise membrane potential—that is, decrease excitability.[10] Whether this potential effect is responsible for the termination of focal atrial tachycardias such as those reported by Perelman and Krikler[18] remains to be established.

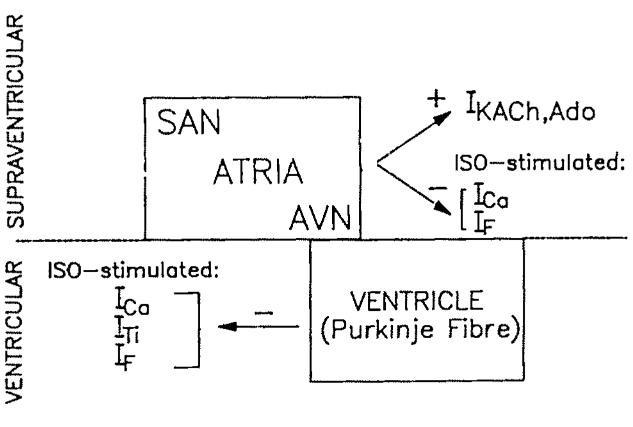

Figure Effect of adenosine on ionic currents of cardiomyocytes. Activation of cardiac adenosine A_1 receptor produces several electrophysiological signals. In supraventricular tissue, including sinoatrial (SA) and atrioventricular (AV) nodes (N), adenosine activates a potassium outward current ($I_{KACh,Ado}$) and antagonises the catecholamine stimulation of calcium inward current (I_{Ca}) and pacemaker current (I_F). In the ventricular myocardium adenosine only antagonises the effects of catecholamines such as isoproterenol (ISO)-stimulated I_{Ca}, I_F, and ISO-induced transient inward current (I_{Ti}).

Also of importance and consistent with its ability to abolish catecholamine-facilitated triggered activity in isolated ventricular myocytes, adenosine has been shown to terminate episodes of ventricular tachycardia in a distinct subset of patients—those with exertion-related sustained ventricular tachycardia and normal hearts.[5] This effect of adenosine seems to be specific for this mechanism of ventricular tachycardia because so far it has been ineffective in ventricular tachycardias thought to be caused by reentry or enhanced automaticity.[5] This important action of adenosine combined with its rather specific effect on the atrioventricular node provides very useful diagnostic information for wide-complex tachycardia as clearly shown in recent studies.[4,6]

A major clinical advantage of adenosine is that its side effects are transitory (seconds) and relatively benign, because of its rapid cellular metabolism. Side effects predominantly include flushing, dyspnoea, and chest pain. Atrioventricular block may also occur, but is seldom symptomatic. Rankin *et al*[6] reported considerably more mild (63%) and severe (36%) side effects with injections of adenosine boluses than did earlier studies, including a recent trial in the United States of 358 patients.[1,2,19] In the earlier studies, the overall incidence of mild side effects was approximately 20–29% and severe side effects <0·5%; all were transient and did not require treatment.[1,2,19] A possible explanation of the discrepancy in the incidence of side effects is that in the study of Rankin *et al*[7] the doses of adenosine used were as high as 20 to 25 mg, whereas in the trial in the-United States[19] the maximum dose was 12 mg. Nevertheless, the fact that adenosine has been shown to terminate paroxysmal supraventricular tachycardia without complications in haemodynamically compromised children is consistent with adenosine's high degree of safety.[3,7]

Conclusion

There are still many potential electrophysiological mechanisms that can account for the antiarrhythmic properties of adenosine; however, further investigation is needed to ascertain not only which of the mechanisms are clinically relevant, but also the pathophysiological role of adenosine in the genesis of disturbances of cardiac rhythm.[20,21] Therefore, the development of selective adenosine related compounds (that is agonists and antagonists) and other modulators may become a fruitful area of investigation that could lead to other approaches to the treatment and diagnosis of cardiac arrhythmias.

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Editorial

Haemodynamic effects of eating

> . . .Those, who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still all this uneasiness vanishes.
>
> WILLIAM HEBERDEN (21 July 1768)[1]

Cardiologists not infrequently find themselves lecturing at evening meetings on the subject of angina pectoris. Many would welcome the opportunity to round off their presentation, before dinner, with one or two well chosen observations on the haemodynamic stresses of eating. Compared with the effects of exercise, mental stress, and cold (on which the lecturer will have talked with authority), eating presents difficulties because published reports are sparse and inconsistent. The cardiologist's experience may be limited to vague recollections of childhood warnings not to go swimming within an hour of eating a meal for fear of potentially fatal cramps in the exercising muscles robbed of their blood supply by the bloated gut (or was it that redirection of blood to exercising muscles would cause violent indigestion?). Further information about these effects comes from three recent studies, two of which appear on pages 22 and 26 of the current issue.[2-4]

The studies

It is reassuring that two articles that rely on widely different methods come to broadly similar conclusions. In a paper published in the *British Heart Journal* of June 1989 Kelbaek *et al* used first pass radionuclide imaging to study left ventricular dimensions before and after a standard Danish meal was eaten.[2] They showed considerable increases in both the end systolic and end diastolic volumes of the left ventricle in healthy volunteers studied in the supine position. The ejection fraction did not increase; but heart rate rose by 17%, stroke volume by 41%, and cardiac output by 62%. The blood pressure did not change; so eating must have caused at least a 50% drop in peripheral vascular resistance, presumably due to vasodilatation in the mesenteric bed.

The group from Nottingham used respiratory gas exchange to estimate cardiac output and, more ambitiously, extended their observations to include exercise tests before and after a meal with subsequent measurements of peripheral blood flow in the calf and forearm (relevant to the swimming dilemma).[3] Again healthy volunteers were studied, but this time they were sitting or standing. The Nottingham meal was marginally more frugal than the Danish one. (It would be interesting and feasible to study the effects of differing meal sizes and compositions—is a snack as bad as a banquet? If not, at what stage does the dose response curve flatten out?) The results showed an increase in cardiac output of 30% after a meal and this differential persisted on exercise. There was a 16% increase in heart rate and no change in blood pressure. There were significant increases both before and after exercise in measures of work done and metabolic activity after eating. Total peripheral vascular resistance fell. Limb blood flow, before and after exercise, however, was not reduced by eating; and since it seems unlikely that other vascular beds became vasoconstricted after food Yi *et al* concluded that eating was haemodynamically stressful. They expressed surprise that more patients with angina and heart failure do not describe a deterioration of their symptoms after a meal. Some clinicians (and that includes me) might agree with William Heberden[1] that angina on exercise after eating is, in fact, quite common. As for deterioration in heart failure, perhaps some parallels can be drawn here between the substantial food-induced drop in peripheral vascular resistance shown in all three studies and the action of the currently fashionable drugs used for the treatment of this condition. Indeed, just such an action is highlighted by Herrlin *et al* whose study of patients with heart failure appears in this issue.[4] The qualitative effects of eating and angiotensin converting enzyme inhibition on cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure are broadly similar.

Questions raised

Like all good studies, these three reports raise many questions. It would be helpful to sort out the mechanisms of these circulatory adjustments. Although plasma catecholamines did not vary before and after food in the Danish study,[2] reference is made to the effects of the autonomic nervous system. Fasting suppresses catecholamine production, presumably to conserve calories, whereas feeding activates the sympathetic system.[5] In an earlier study, similar to their current one, Kelbaek *et al* showed that the stroke volume and heart rate increased after a meal both at rest and on upright exercise. The increase in stroke volume, but not heart rate, was inhibited by autonomic blockage with metoprolol and atropine. Plasma concentrations of adrenaline were unaffected by eating, so these workers concluded that parasympathetic withdrawal may be important in the postprandial changes that they observed.[6] Hormonal factors may also have a role—for example infusion of vasoactive intestinal polypeptide causes a considerable reduction of peripheral vascular resistance, drop in blood pressure, and compensatory tachycardia. Cardiac output rises considerably.

Whatever mechanisms underlie these interesting haemodynamic changes, clinicians will be anxious to see whether they are affected by the altered conditions associated with disease states. Published reports are inconsistent, possibly because of differences in meal composition and the mode of exercise (upright/supine). One study confirmed the increase in heart rate after a meal in subjects with postprandial angina, who also had a larger blood pressure response on exertion.[7] Angina developed more rapidly when these patients were exercising after a meal. The double product (systolic blood pressure × heart rate) at the onset of pain was the same before and after the meal. This strongly suggests that the harmful effects of eating are more likely to be the result of haemodynamic stress rather than the diversion of blood away from the coronary arteries to other vascular beds.

It would be intesting to compare the haemodynamic effects of eating in angina patients whose symptoms are or are not aggravated by food. How are these effects modified by β blockers, prophylactic nitrates, and different calcium antagonists? Theoretically β blockers should be helpful whereas food might attenuate the value of nitrates.

Some data have been published on the haemodynamic effects of eating in patients with left ventricular failure. In one such study, heart rate and cardiac output increased after eating, but mean blood pressure fell.[8] In another study the ejection fraction in patients with moderate ventricular dysfunction increased after a meal.[9] The observed effects did not seem to be particularly detrimental and were similar to those reported in the current study by Herrlin *et al*. These changes were accentuated by angiotensin converting enzyme inhibition but were also quite considerable in a group treated with placebo. Any study of vasodilator treatment that does not take account of these basal fluctuations is likely to be seriously flawed.

Advice

All patients with angina should be advised to avoid exertion after eating. Perhaps an hour is sufficient (the current observations were made at 30 minutes) though haemodynamic changes have been seen as long as six hours after a meal. Significant changes were still present 2–4 hours after eating in heart failure patients treated with placebo. Further information is needed before drug treatment can be tailored to a specific requirement and appropriate advice given on the size and content of the meal least likely to provoke angina. Meanwhile, the well informed lecturer might conclude by inviting the audience to reflect on the negative inotropic effect that healthy people show after drinking alcohol.[10]

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ORIGINAL ARTICLES

Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patients

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Abstract

Thallium tomographic imaging and exercise electrocardiography were performed on 136 diabetic patients without symptoms of heart disease. Thirty three patients had post-exercise thallium defects and 19 had ST 1 mm ≥ segment depression during exercise electrocardiography. Both tests were positive in 13 patients. Coronary angiography was subsequently performed on 33 patients with either scintigraphic and/or electrocardiographic evidence of myocardial ischaemia. Angiographically significant coronary artery disease (≥50% narrowing of the coronary artery lumen) was detected in 13 patients. Six patients had minimal coronary artery stenosis (<50%), and 14 had normal coronary arteries. Six patients refused cardiac catheterisation. In 14 out of 27 patients with post-exercise thallium defects coronary angiography did not show any coronary artery stenoses (positive predictive accuracy 48%). Exercise electrocardiography showed only one false positive result (positive predictive accuracy 94%) but failed to detect coronary artery disease in three patients with a positive scintigraphic result.

The accuracy of a positive exercise electrocardiographic test seems to be better than that of a positive thallium tomographic scan for detecting asymptomatic coronary artery disease in diabetic patients. The high number of false positive thallium defects may be the result of technical features inherent in thallium tomography and/or the possible disease of the small intramyocardial arteries in diabetic patients.

Heart disease is a major cause of mortality and morbidity in diabetic patients[1] and coronary artery disease is more common in diabetic patients.[2] Silent myocardial infarctions are common and myocardial ischaemic episodes often tend to be asymptomatic in diabetic patients.[3-5] Recent studies suggest that silent myocardial ischaemia may be accompanied by increased mortality,[6 7] and hence non-invasive tests have been recommended to detect asymptomatic coronary artery disease. We evaluated the usefulness of thallium tomographic imaging and exercise electrocardiography for detecting coronary artery disease in a population of diabetic patients without symptoms of heart disease.

Patients and methods

PATIENTS

The diabetic patients were selected from the patient register of Oulu University Central Hospital and the membership register of the local diabetic association. Table 1 presents their clinical data. Those classified as having type I diabetes (insulin dependent diabetes mellitus, n = 70) had had diabetes and a tendency to ketosis from an early age, while those classified as type II diabetic patients (non-insulin dependent diabetes mellitus, n = 66) were treated with a diet alone or with a diet combined with oral hypoglycaemic agents. Patients with type II diabetes were not liable to ketosis and showed considerable C-peptide activity after glucagon stimulation. All the diabetic patients fulfilled the World Health Organisation criteria for idiopathic diabetes mellitus. We studied 50 women and 86 men.

The exclusion criteria were: (*a*) age <35 or >60; (*b*) duration of type I diabetes <5 years; (*c*) known ischaemic heart disease; (*d*) symptoms of ischaemic heart disease according to the Rose questionnaire; (*e*) antilipidaemic medication; (*f*) severe renal disease (serum creatinine >200 mmol/l); (*g*) uncontrolled retinopathy; (*h*) thyroid disease, overt malignant tumours, alcoholism; and (*i*) any severe disease that could be contraindication for the maximal exercise test.

All the patients gave their informed consent and the investigation was approved by the ethics committee of the Faculty of Medicine at the University of Oulu.

METHODS

Eligible patients were examined by maximal exercise electrocardiography and exercise thallium tomographic imaging. If either of these non-invasive tests showed signs of myocardial ischaemia the patient was recalled for cardiac catheterisation.

Table 1 Clinical characteristics of the diabetic patients (mean (SD))

	IDDM *(n = 70)*	*NIDDM* *(n = 66)*	*Both* *(n = 136)*
Age (yr)	46·3 (7·3)	49·4 (6·8)	47·8 (7·2)
Sex (F/M)	31/39	19/47	50/86
Duration of diabetes (yr)	13 (8)	10 (6)	12 (7)
Treatment of diabetes:			
Insulin	69 (99%)	15 (23%)	84 (62%)
Insulin and oral hypoglycaemic agents	1 (1%)	1 (2%)	2 (1%)
Oral hypoglycaemic agents		26 (39%)	26 (19%)
Diet only		24 (36%)	24 (18%)
Glycated haemoglobin A_1 (%)	11·4 (2·3)	11·0 (2·7)	11·3 (2·5)
Blood glucose (mmol/l)	11·0 (3·7)	10·7 (3·9)	10·9 (3·8)
Serum cholesterol (mmol/l)	5·8 (1·0)	5·9 (1·2)	5·8 (1·1)

IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus

Exercise electrocardiography

A maximal exercise test was performed on an electrically braked bicycle ergometer, starting at a workload of 30 W which was increased every minute by 15 W for men and 10 W for women. The final workload was the individual maximum determined by age or fatigue. The maximal heart rate was calculated on the basis of the following equation: $205 - 1/2 \times \text{age}$. The target was to achieve at least 85% of this maximal heart rate. A 12 lead electrocardiogram was recorded before the test and at the end of every second minute during it and up to five minutes afterwards. More frequent recordings were made if electrocardiographic signs, abnormal blood pressure reactions, or any symptoms developed. A test was regarded as positive if there were ST depressions of $\geqslant 1$ mm that were planar or downsloping and persisted for 0·08 s after the J point.

Thallium-201 scintigraphy

Thallium scintigraphy was performed one day after exercise electrocardiography according to the same exercise protocol. Three mCi (110 MBq) of thallium-201 was injected intravenously 30–60 seconds before the end of the ergometric exercise. Thallium imaging was started within 5 minutes of the end of the bicycle test and was repeated after about 4 hours' rest. A detailed description of the thallium tomographic imaging method has been given earlier.[8] Data acquisition was carried out with a Siemens Rota ZLC 75 gamma camera with a low energy, all purpose collimator. Thirty images at each of 6 grades were acquired for 35 seconds each to form a matrix of 64 × 64 elements. Total acquisition time was 20 minutes. Data collection began from the posterior oblique view and ended at the right anterior oblique view. The transaxial sections were reconstructed by filtered back-projection with the Gamma-11 computer system. No attenuation correction was performed. Each reconstructed slice was 12 mm thick. Coronal and sagittal tomograms were reorganised from the set of transaxial tomograms corresponding to transverse and longitudinal sections of the cardiac axis. The tomographic slices were stored as *x* rays for later analysis.

The images for each patient were examined by two different observers without knowledge of the angiographic information. Five discrete regions of the left ventricular myocardium—anterior, septal, apical, inferior and posterolateral—were defined. Regional perfusion was regarded as abnormal if a defect could be seen in at least two tomographic sections with or without redistribution. The thallium defects were graded as mild, moderate, or severe by visual interpretation of the images. Complete agreement between the observers about the presence or absence of coronary artery disease was achieved in 125 (92%) cases and a consensus was obtained by discussion in the remaining 11 (8%) cases.

Cardiac catheterisation

All the patients who showed signs of myocardial ischaemia in the above non-invasive tests were recalled for cardiac catheterisation. Six of the 39 refused to undergo this procedure. The remaining 33 patients underwent left sided cardiac catheterisation, including selective coronary arteriography in multiple projections comprising caudal and cranial views obtained by the Judkins technique. Biplanar left ventricular cineangiograms were taken as described earlier.[9] A reduction of $\geqslant 50\%$ of luminal diameter was regarded as a significant lesion. The angiographic findings were interpreted by two experienced observers.

Results

EXERCISE ELECTROCARDIOGRAPHY AND SCINTIGRAPHY DATA

One hundred and three patients (76%) reached 85% of the maximum heart rate predicted for their age during the bicycle exercise test while the remaining 33 (24%) stopped because of fatigue without reaching this maximum. None of the patients had angina or chest pain during the stress test. Nineteen patients (14%) had $\geqslant 1$ mm ST depression during or after exercise and 117 (86%) had a normal electrocardiographic response to exercise. Thirty three patients (24%) had defects in the post-exercise thallium tomographic images, these being reversible in 23 (16 mild, five moderate, two severe), fixed in eight (six mild, one moderate, one severe), and diffuse reductions of thallium uptake in two. Figure 1 shows an example of thallium tomographic images from a symptom free patient with three vessel disease in coronary angiography. The haemodynamic responses were similar in patients during exercise electrocardiography and thallium scintigraphy (table 2).

RELATION BETWEEN CORONARY ANGIOGRAPHY FINDINGS AND RESULTS OF THE NON-INVASIVE TESTS

Thirteen patients had coronary artery stenosis ($\geqslant 50\%$ narrowing), six had coronary artery narrowings of $<50\%$, and 14 had angiographically normal coronary arteries. Three patients had three vessel disease, five patients had two vessel disease, and five patients had one vessel disease. Table 3 shows the relations between the angiographic findings and the results of non-invasive tests. Fourteen of 27 patients with positive scintigraphic results had normal findings at coronary angiography (positive predictive accuracy 48%), while only one of 17 patients with positive exercise

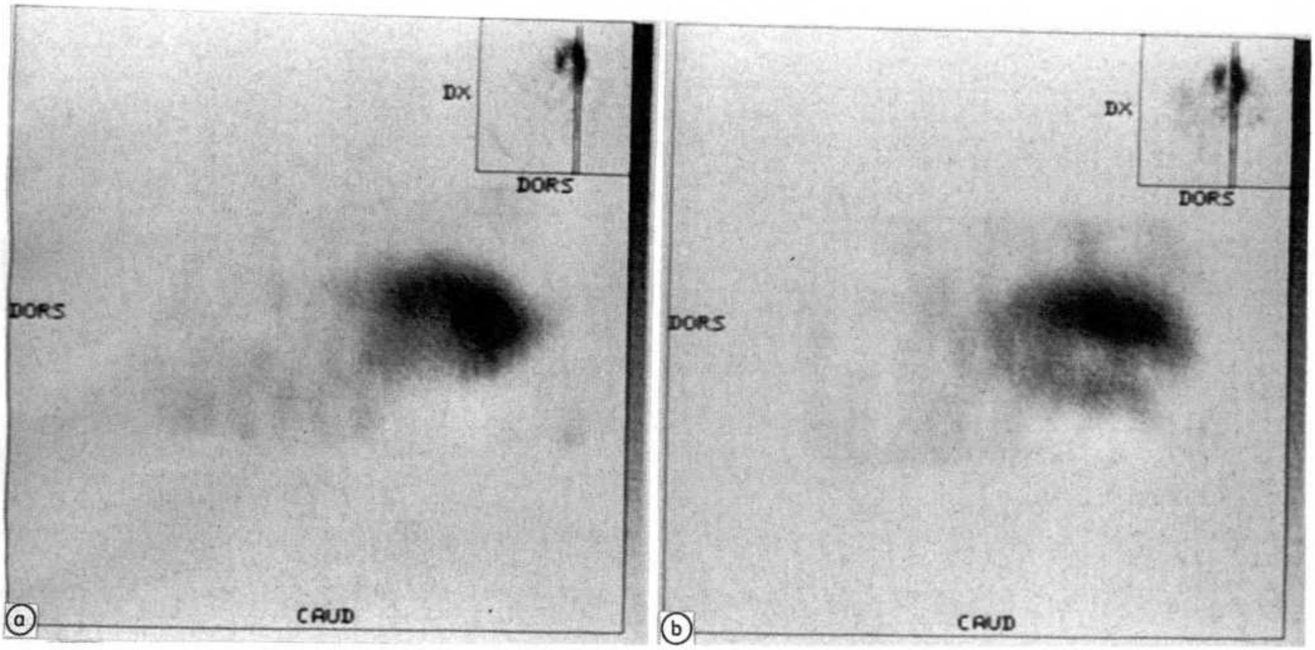

Figure 1 An example of thallium tomographic images in a symtom free patient with three vessel disease detected by coronary angiography. There were reversible defects in the inferoposterior and apical regions of the left ventricle. Sagittal sections (a) at rest and (b) after dynamic exercise.

electrocardiography had normal coronary angiography (positive predictive accuracy 94%).

Nine (eight mild, one moderate) out of 14 false positive defects were reversible and five (mild) defects were fixed. Five (mild) out of the 14 false positive defects were in the anterior region, four (three mild, one moderate) in the inferior region, two (mild) in the septal region, one (mild) in the posterior region of the left ventricle, and two defects were diffuse reductions of thallium uptake. Figure 2 shows a false positive thallium scan.

There were two patients with a positive thallium scan and negative exercise electrocardiography who had significant coronary artery stenoses and one who had insignificant stenoses. Conversely there were three patients with positive exercise electrocardiography and negative thallium scan who had significant coronary artery stenoses and three patients who had insignificant coronary artery stenoses. One patient with a false negative exercise electrocardiogram had two vessel coronary artery disease and the other had one vessel disease, whereas one patient with negative thallium scintigraphy

Table 2 Haemodynamic data during exercise electrocardiography and thallium scintigraphy in the catheterised patients

	Exercise electrocardiography					*Thallium scintigraphy*				
	Heart rate (beats/min)		*SBP (mm Hg)*			*Heart rate (beats/min)*		*SBP (mm Hg)*		
Case no	*Rest*	*Exercise*	*Rest*	*Exercise*	*Load(max) (W)*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Load(max) (W)*
1	078	165	140	200	090	083	155	170	195	090
2	069	131	145	180	120	135	165	110	160	110
3	115	178	130	210	180	095	160	120	230	195
4	095	155	195	270	195	100	150	180	260	180
5	076	160	105	180	090	090	160	125	150	090
6	067	153	130	210	210	080	160	105	190	210
7	076	171	130	230	120	080	170	160	210	130
8	100	172	180	240	180	090	129	150	220	135
9	075	165	150	220	210	073	145	110	220	195
10	110	178	170	185	070	125	175	185	220	080
11	053	156	145	190	165	074	125	125	210	150
12	071	171	145	240	255	080	165	120	210	240
13	063	154	160	210	195	055	155	145	170	195
14	078	150	150	215	225	074	136	150	220	195
15	063	150	135	230	225	064	142	100	185	225
16	085	123	170	190	070	096	130	130	200	120
17	072	145	120	180	180	087	150	150	200	195
18	069	170	130	220	255	070	152	120	210	255
19	090	166	130	210	100	090	162	155	190	100
20	057	170	180	240	240	066	165	150	230	240
21	085	170	140	210	195	100	160	140	190	225
22	064	112	155	125	120	059	108	155	145	120
23	090	153	155	200	120	088	155	120	170	150
24	080	155	155	210	165	070	140	110	230	180
25	072	150	130	210	120	085	142	130	185	120
26	085	133	140	240	135	081	125	160	210	135
27	091	106	130	170	130	098	160	120	170	140
28	065	160	165	240	120	095	168	140	230	120
29	081	153	160	200	180	082	130	160	190	180
30	066	182	110	175	195	095	180	110	175	195
31	084	168	125	180	210	079	158	120	190	210
32	115	163	145	240	180	100	138	150	260	120
33	076	173	130	185	210	064	150	140	210	135

SBP, systolic blood pressure.

Table 3 Relation between coronary angiographic findings and results of positive exercise electrocardiography and/or thallium scintigraphy

Diseased coronary arteries	*Positive thallium scintigraphy*	*Negative thallium scintigraphy*	*Positive exercise ECG*	*Negative exercise ECG*
Refused angiography	6	0	2	4
None	14	0	1	13
Minimal narrowings	3	3	5	1
1 vessel disease	3	2	4	1
2 vessel disease	4	1	4	1
3 vessel disease	3	0	3	0

ECG, electrocardiogram.

had two vessel disease and two patients had one vessel disease.

There were 11 catheterised patients with both positive thallium scintigraphy and exercise electrocardiography. Eight out of these patients had significant coronary artery stenoses, two had insignificant narrowing, and one had normal coronary arteries.

Discussion

Thallium tomographic imaging showed perfusion defects in a high proportion of diabetic patients without symptoms of heart disease. These results are consistent with a previous survey in which 42% of symptom free diabetic men had positive thallium scans,[10] although this study did not relate the thallium results to coronary angiographic findings.

In the present study, thallium tomographic imaging showed perfusion defects in 24% of patients. Perfusion defects were commonly detected when coronary angiography showed a normal epicardial coronary artery anatomy. Some of the false positive thallium scintigraphic results may be the result of technical features inherent in thallium tomography, such as breast artefacts, inaccurate patient positioning between imaging phases, diaphragmatic attentuation of the inferior cardiac wall, abnormal apical thinning, computer processing errors, or obesity.[11] Thallium defects in the false positive scans were usually mild and reversible. The visual interpretation between mildly defective and normal thallium uptake is highly subjective, which may partly explain the present results. Quantitative analysis of the images might reduce or increase the number of false positive scans.

One explanation for the false positive results is the possibility of disease of the small intramyocardial arteries with diabetes, which may result in perfusion defects even when the epicardial coronary artery anatomy is normal. Two patients with normal coronary anatomy had diffuse irregularities in thallium uptake, which may actually be caused by small vessel disease or diabetic cardiomyopathy. Furthermore, visual interpretation of the coronary arteries may not be a reference standard for non-invasive tests,[12] a fact which may also partly explain the low positive predictive accuracy of thallium imaging. In fact we found perfusion defects in three and electrocardiographic evidence of myocardial ischaemia in five out of six patients in whom coronary narrowings was interpreted as minimal (<50%). We know of no other evaluations of the positive preditive accuracy of single photon emission computed tomography in a large series of symptom free patients. When we used the imaging method described, we found a high sensitivity and specificity of thallium tomographic method in different patient populations.[8 13] The present data further emphasise the need for validating the new non-invasive tests in patient populations with different pre-test probabilities of myocardial ischaemia.[14]

An abnormal exercise electrocardiogram is more common in diabetic than in non-diabetic patients. The prevalence of abnormal ST segment changes has been estimated to be 20–23% in symptom free diabetic populations[4 15 16] and 2–13% in other symptom free populations.[17] The prevalence of abnormal exercise electrocardiography was 14% in this study. The predictive accuracy for abnormal exercise elec-

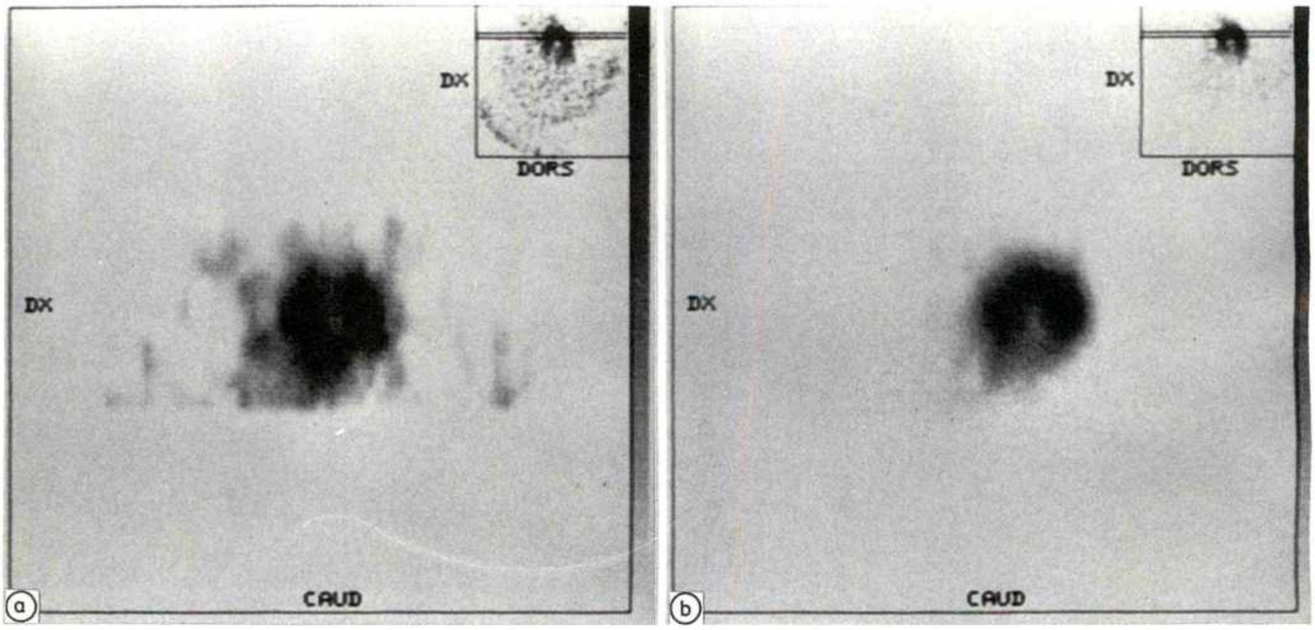

Figure 2 An example of a false positive thallium scan in a patient with normal coronary angiography. A reversible defect in the inferoposterior region of the left ventricle. Coronal sections (a) at rest and (b) after dynamic exercise.

trocardiography in symptom free cohorts has been reported to be only 20%.[18] On the contrary, the positive predictive accuracy of exercise electrocardiography was as high as 94% in the present series. According to Bayes' theorem the predictive value varies with the prevalence of disease.[19] We studied mostly male, middle aged and elderly diabetic patients. In this type of population the prevalence of coronary artery disease is high, perhaps explaining the high predictive accuracy of exercise electrocardiography in the present study.

The predictive accuracy of exercise electrocardiography was better than that of thallium imaging but it still failed to detect three patients with coronary artery disease. These results accord with previous observations that exercise electrocardiography may have a low sensitivity for detecting coronary artery disease.[20 21] In the present study we could not calculate the absolute sensitivity and specificity of these methods, because this would have required all the patients to be catheterised.

Screening of certain high risk populations has recently been proposed for detecting coronary artery disease, because of the possibility of silent myocardial ischaemia.[18 22 23] The present findings suggest that thallium tomographic imaging may not be a particularly useful non-invasive screening method in symptom free diabetic patients because of its low positive predictive accuracy. The accuracy of a positive exercise electrocardiogram is higher, but it may have lower sensitivity.

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Diagnostic significance of gadolinium-DTPA (diethylenetriamine penta-acetic acid) enhanced magnetic resonance imaging in thrombolytic treatment for acute myocardial infarction: its potential in assessing reperfusion

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Abstract

The diagnostic value of gadolinium-DTPA (diethylenetriamine penta-acetic acid) enhanced magnetic resonance imaging in patients treated by thrombolysis for acute myocardial infarction was assessed in 27 consecutive patients who had a first acute myocardial infarction (14 anterior, 13 inferior) and who underwent thrombolytic treatment and coronary arteriography within 4 hours of the onset of symptoms. Magnetic resonance imaging was performed 93 hours (range 15–241) after the onset of symptoms. A Philips Gyroscan (0·5 T) was used, and spin echo measurements (echo time 30 ms) were made before and 20 minutes after intravenous injection of 0·1 mmol/kg gadolinium-DTPA. In all patients contrast enhancement of the infarcted areas was seen after Gd-DTPA. The signal intensities of the infarcted and normal values were used to calculate the intensity ratios. Mean (SD) intensity ratios after Gd-DTPA were significantly increased (1·15 (0·17) *v* 1·52 (0·29)). Intensity ratios were higher in the 17 patients who underwent magnetic resonance imaging more than 72 hours after the onset of symptoms than in the 10 who underwent magnetic resonance imaging earlier, the difference being significantly greater after administration of Gd-DTPA (1·38 (0·12) *v* 1·61 (0·34)). When patients were classified according to the site and size of the infarcted areas, or to reperfusion (n = 19) versus non-reperfusion (n = 8), the intensity ratios both before and after Gd-DTPA did not show significant differences.

Magnetic resonance imaging with Gd-DTPA improved the identification of acutely infarcted areas, but with current techniques did not identify patients in whom thrombolytic treatment was successful.

Magnetic resonance imaging of the heart offers the potential for the non-invasive detection, localisation, and measurement of acutely infarcted myocardial areas.[1-3] Infarcted areas can be identified by local wall thinning, increased flow signal in the ventricular cavity, and increased signal intensity in the infarcted area.[4,5] In particular T_1 and T_2 relaxation times are prolonged in the oedematous infarct zone.[6-8] T_2 prolongation seems to predominate and therefore an increased myocardial signal intensity is best appreciated on T_2 weighted images obtained by long repetition times and long echo times with the multi-echo technique in a spin echo sequence.[2,3,9] However, in many cases the contrast has been suboptimal because of the inherent low signal to noise ratio. Recently, the use of gadolinium (Gd)-diethylenetriamine penta-acetic acid (DTPA) as a paramagnetic contrast agent has been proposed for better delineation of areas of infarcted myocardium.[10-12] Gd-DTPA significantly shortened the T_1 relaxation time of irreversibly injured canine myocardium and so increased the signal intensity of the infarct in relation to normal myocardium.[13-15] Previous studies in patients with acute myocardial infarction have shown that administration of Gd-DTPA resulted in significant contrast enhancement of infarcted myocardial areas, with maximal contrast enhancement being obtained 20–30 minutes after administration.[12,16] Experimental studies have shown that Gd-DTPA enhanced magnetic resonance imaging can distinguish between reperfused and non-reperfused myocardium in acute myocardial infarction.[17-19] This might be of clinical importance because currently there are no reliable methods of assessing the results of coronary thrombolysis non-invasively. To test this diagnostic potential we examined the results of magnetic resonance imaging before and after administration of Gd-DTPA in 27 patients with acute myocardial infarction who underwent coronary arteriography and intracoronary administration of streptokinase within 4 hours of the onset of symptoms and in whom we therefore had unequivocal evidence on the occurrence of early reperfusion. As well as the effect of reperfusion we evaluated the influence of infarct size and site on myocardial signal intensity and we determined the time period in which Gd-DTPA gave the greatest enhancement.

Patients and methods

PATIENTS

Twenty seven patients (23 men, four women; mean age 52 years (range 30–75)) with acute myocardial infarction were studied by electrocardiographically gated magnetic resonance

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Individual results of streptokinase treatment and magnetic resonance imaging findings

Case	*Age (yr) and sex*	*Infarct site*	*Infarct artery*	*Residual stenosis (%)*	*Cumulative HBDH (U/l)*	*Time to reperfusion (min)*†	*From infarct to MRI (h)*	*IR before Gd-DTPA*	*IR after Gd-DTPA*	*ΔIR (%)*	*Aspect contrast*
1	57 M	Inf	RCA	91–99	664	55	98	1·03	1·43	44	II
2	30 M	Inf	LCX	50–90	2018	105	46	0·93	1·29	39	II
3	56 M	Inf	LCX	50–90	542	105	41	1·01	1·29	28	*
4	46 M	Ant	LAD	0–50	105	115	97	1·07	1·24	16	0
5	46 M	Ant	LAD	50–90	1230	130	63	1·06	1·23	16	*
6	47 M	Ant	LAD	0–50	1331	145	110	1·35	1·44	7	II
7	49 F	Inf	RCA	91–99	590	150	99	1·15	1·21	5	II
8	42 F	Inf	RCA	0–50	296	150	82	1·00	1·46	46	II
9	33 M	Inf	RCA	91–99	534	160	113	1·15	1·31	14	I
10	65 M	Ant	LAD	0–50	1471	160	119	1·07	1·73	63	I
11	51 M	Ant	LAD	50–90	2137	170	48	1·11	1·41	27	II
12	57 M	Inf	RCA	91–99	2108	180	120	1·18	1·32	12	II
13	41 M	Ant	LAD	0–50	1234	185	241	1·27	1·58	24	I
14	60 M	Ant	LAD	0–50	1374	200	37	1·02	1·63	60	II
15	39 M	Ant	LAD	0–50	1051	210	97	1·36	2·13	57	II
16	68 F	Ant	LAD	0–50	387	210	88	1·65	2·55	55	II
17	75 M	Inf	RCA	91–99	822	240	44	0·94	1·31	39	I
18	58 M	Inf	LCX	0–50	822	240	99	1·44	1·74	21	I
19	50 M	Inf	RCA	0–50	1061	180	64	1·28	1·40	9	II
20	59 M	Ant	LAD	100	1745	—	109	1·00	1·80	80	II
21	49 M	Inf	LCX	100	685	—	179	1·09	1·52	38	II
22	75 M	Inf	RCA	100	1238	—	51	1·15	1·38	20	I
23	70 F	Ant	LAD	100	1509	—	15	0·86	1·31	52	II
24	46 M	Ant	LAD	100	562	—	95	1·13	1·66	47	II
25	38 M	Ant	LAD	100	282	—	58	1·13	1·51	34	II
26	51 M	Ant	LAD	100	1350	—	167	1·15	1·45	26	II
27	61 M	Inf	LCX	100	1135	—	134	1·38	1·73	25	II
Mean	52				1048		93	1·15	1·52	33	
SD	11				566		49	0·17	0·29	19	

Ant, anterior, HBDH, hydroxybutyrate dehydrogenase, inf, inferior, IR, intensity ratio infarct/normal tissue, ΔIR = percentage change in intensity ratio, LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery, MRI, magnetic resonance imaging; RCA, right coronary artery, 0 = no contrast enhancement; I = homogeneous contrast enhancement, II = inhomogenous contrast enhancement. *Poor image quality †Time from streptokinase infusion to reperfusion in minutes

imaging 93 hours (range 15–241) after the acute event (table). Seventeen patients were included in previous related studies.[20 21] In all patients a first transmural myocardial infarction was diagnosed on the basis of electrocardiographic Q waves and a typical increase in cardiac enzymes. Immediately after electrocardiographic evidence of acute myocardial infarction was obtained, an intravenous dose of 750 000 U of streptokinase was given. The coronary arteriography was performed within 4 hours of the onset of symptoms. At catheterisation, an additional dose of 250 000 U streptokinase was usually administered into the infarct related artery. In 19 patients reperfusion was achieved; in eight patients the infarct related artery remained occluded. Ten patients underwent magnetic resonance imaging studies within 72 hours of the onset of symptoms (mean 47 hours, range 15–64 hours; group 1) and 17 patients underwent magnetic resonance imaging studies >72 hours (mean 120 hours, range 82–241 hours) (group 2) after the onset of symptoms. The cut off point of 72 hours was based on our policy to perform percutaneous coronary transluminal angioplasty within 72 hours in patients with signs and symptoms of residual ischaemia after thrombolytic treatment. Anterior wall infarction was present in 14 patients and inferior wall infarction in 13 patients. To measure infarct size we used cumulative α hydroxybutyrate dehydrogenase release up to 72 hours after the onset of symptoms.[22] In our study, mean α hydroxybutyrate dehydrogenase release was 1048 U/l (range 105 to 2136 U/l). Patients with an α hydroxybutyrate dehydrogenase release of <1000 U/l were considered to have small to moderate infarctions (12 patients, mean 492 U/l, range 105 to 822 U/l). Fifteen patients had large infarctions (>1000 U/l, mean 1432 U/l, range 1051 to 2137 U/l).

MAGNETIC RESONANCE IMAGING TECHNIQUE

The magnetic resonance imaging studies were performed with an 0·5 T Philips Gyroscan. Four 10 mm thick slices were taken at a 5 mm slice interval. Sagittal planes were chosen for

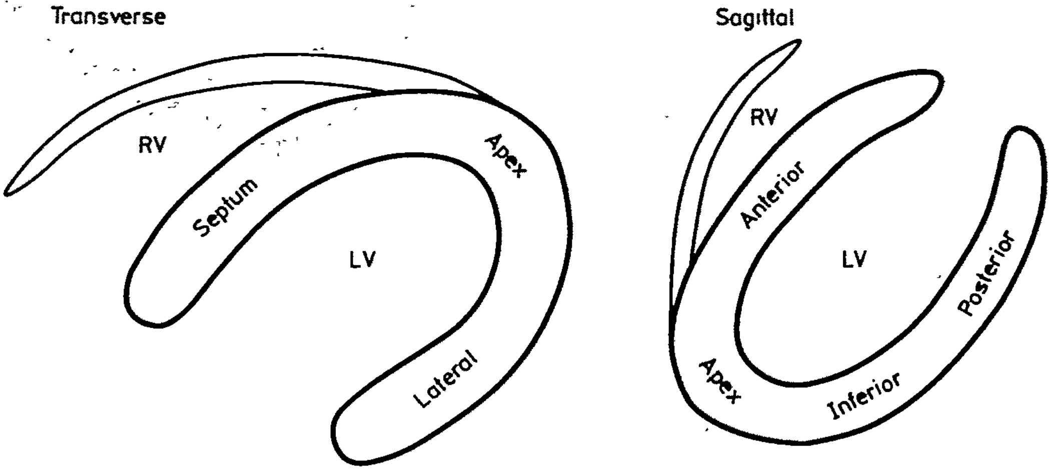

Figure 1 Planes used for detection of myocardial infarction (transverse planes for anteroseptal infarction and sagittal planes for inferior infarction. LV, left ventricle, RV, right ventricle.

anterolateral or inferior infarction, and transverse planes for anteroseptal or posterolateral infarction (fig 1). The echo times were 30 ms and the repetition times were equal to the RR interval. The trigger delay was 200 ms after the R wave of the electrocardiogram. A matrix of 128 × 256 pixels was used for acquisition and the images were displayed with a 256 × 256 matrix. The field of view was 30–40 cm.

After the baseline magnetic resonance imaging scans were performed, all patients received an intravenous injection of 0·1 mmol Gd-DTPA/kg body weight. Since our previous studies showed maximal contrast in the first 15–25 minutes after Gd-DTPA administration,[16 20 21] the magnetic resonance imaging scans were repeated about 20 minutes after the administration of Gd-DTPA.

IMAGE ANALYSIS

The magnetic resonance imaging scans were visually assessed for the presence of signs indicative of myocardial infarction. The region with maximal contrast enhancement was considered to represent the infarcted area and the region without visual contrast enhancement was considered to represent normal myocardial tissue. The images were read by two independent observers blinded to patient identity. When they disagreed a third observer was consulted to reach a consensus. Quantitative evaluation of contrast enhancement was also performed by computer assisted determination of signal intensities. Signal intensities from the post-contrast images were obtained by region of interest analysis from adjacent myocardial regions, usually 10 per slice (about 1 cm^2 per region). Based on the signal intensities obtained, intensity versus region curves were constructed and the region with maximal signal intensity after Gd-DTPA was regarded as representing the infarcted area. Signal intensity ratios were calculated by dividing the maximal signal intensity by the signal intensity from a normal non-infarcted region. Signal intensities were normalised for the increase in the non-infarcted areas, which was shown to be around 20%.[23] For optimal comparison of changes in the intensity ratios of the pre-contrast and post-contrast images, we selected the regions on the post-contrast image that were similar on the time-activity curve obtained from the pre-contrast image. We also dichotomised our patients according to the morphological appearance of the contrast enhancement based on experimental findings by Peshock *et al.*[19] Homogeneous contrast enhancement is considered to represent reperfusion and was called type I in our study (fig 2), and inhomogeneous enhancement, reportedly representing non-reperfusion, was called type II (fig 3).

STATISTICAL ANALYSIS

Statistical analysis was performed with the multiple *t* test and Bonferroni's correction.

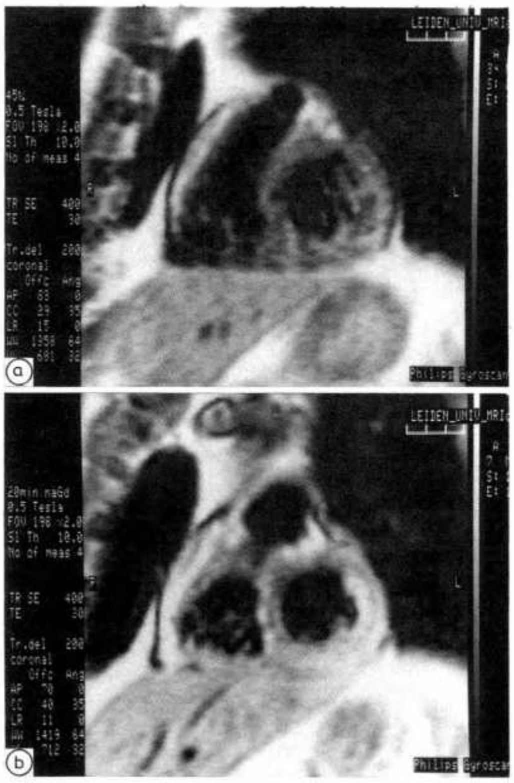

Figure 2 Sagittal image before (a) and after (b) administration of Gd-DTPA in a patient with an inferoposterior wall infarction and successful recanalisation of the right coronary artery. Twenty minutes after Gd-DTPA administration homogeneous contrast enhancement (type I) was seen in the inferoposterior region of the myocardium, reportedly representing reperfusion.[19] Also the non-infarcted segments showed an increase in contrast enhancement.

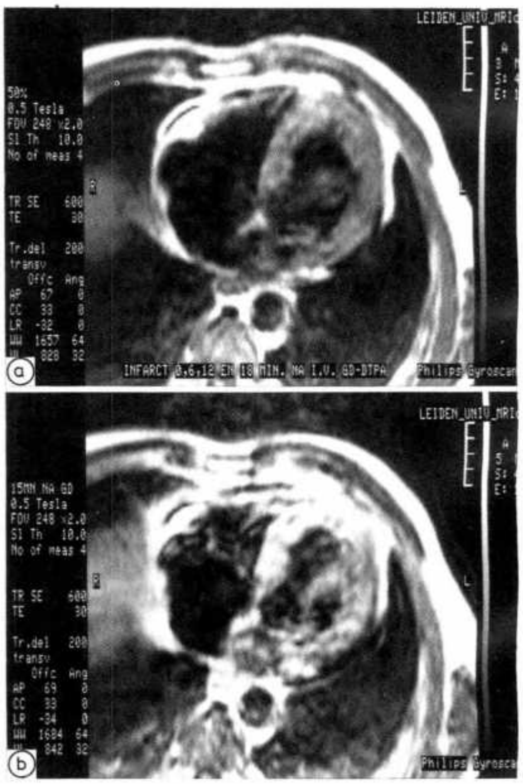

Figure 3 Tranverse image before (a) and after (b) administration of Gd-DTPA in a patient with an anteroseptal wall infarction. The left anterior descending coronary artery remained occluded after intracoronary streptokinase. Fifteen minutes after Gd-DTPA administration inhomogeneous contrast enhancement (type II) was seen in the anteroseptal region of the myocardium, reportedly representing non-reperfusion.[19] Like figure 2 the non-infarcted segments showed an increase in contrast enhancement.

Non-parametric correlation analysis was performed with Spearman rank test. A p value of < 0·05 was considered to be significant. Values are expressed as the mean (SD).

Results

The table shows the results of thrombolytic treatment and the magnetic resonance imaging findings in each patient. After the administration of Gd-DTPA 24 patients (89%) showed increased contrast enhancement in the infarcted areas, which improved infarct definition. The site of the region with contrast enhancement always coincided with the infarct site established by the electrocardiogram. Also the non-infarcted areas showed a slight but definite increase of contrast after Gd-DTPA (figs 2 and 3). In one patient (case 4) no contrast enhancement was seen; this was probably because the infarct was small (α hydroxybutyrate dehydrogenase release of 105 U/l). In two patients (cases 3 and 5) poor quality magnetic resonance imaging did not allow adequate visual interpretation. Despite the absence of visually observed contrast enhancement in three patients, all 27 patients showed an increase of computer-assessed intensity ratios after Gd-DTPA (1·15 (0·17) *v* 1·52 (0·29) (p < 0·001)). The area with the computer-assessed maximal signal intensity ratio after Gd-DTPA was always within the areas of maximal signal enhancement by visual assessment.

The intensity ratio before Gd-DTPA in the patients who were studied early (group 1) (1·06 (0·12)) was not significantly different from that in the patients who were studied late (group 2) 1·19 (0·18). After administration of Gd-DTPA patients in group 1 showed intensity ratios of 1·38 (0·12) and those in group 2 1·61 (0·34) (p < 0·05) (fig 4). There was a significant correlation between time to magnetic resonance imaging and intensity ratio after Gd-DTPA (Spearman rank correlation coefficient: 0·34; p < 0·05).

Infarct size had no significant effect on signal intensities. Before administration of Gd-DTPA the intensity ratios of the patients with small to moderate infarcts (α hydroxybutyrate dehydrogenase release < 1000 U/l) were 1·15 (0·20) and the intensity ratios of the patients with a large infarct size (α hydroxybutyrate dehydrogenase release > 1000 U/l) were 1·14 (0·16) (p = NS). After administration of Gd-DTPA the small infarct size group showed intensity ratios of 1·52 (0·36) *v* 1·52 (0·24) (p = NS) in the large infarct size group (fig 5).

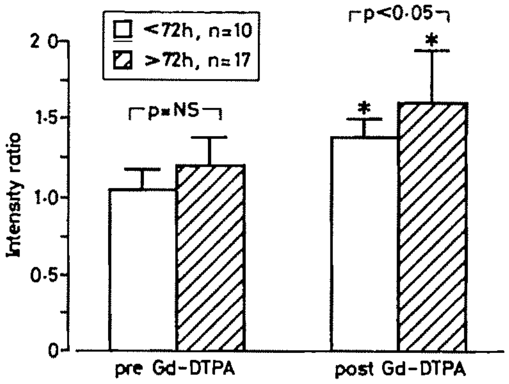

*Figure 4 Intensity ratio before and after Gd-DTPA administration when magnetic resonance imaging was early (within 72 hours) and when it was late (more than 72 hours after acute onset of symptoms). After Gd-DTPA the intensity ratio in late magnetic resonance imaging was significantly higher than in early magnetic resonance imaging (p < 0·05). Within each group the signal intensity ratio increased significantly after Gd-DTPA administration (*p < 0·001).*

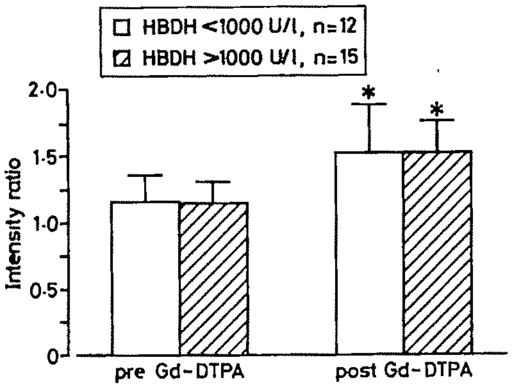

*Figure 5 Intensity ratio before and after Gd-DTPA administration in relation to infarct size (small to moderate infarct size (hydroxybutyrate dehydrogenase (HBDH) release < 1000 U/l) versus large infarct size (HBDH release > 1000 U/l). There was no significant effect of infarct size on signal intensity ratio before or after Gd-DTPA administration. Within each group the intensity ratio increased significantly after Gd-DTPA administration (*p < 0·001).*

There were no differences in intensity ratios between patients with an anterior wall infarction and those with inferior wall infarction. Before administration of Gd-DTPA the intensity ratios were 1·16 (0·19) and 1·13 (0·16) in anterior and inferior wall infarction respectively, and after Gd-DTPA the intensity ratios were 1·62 (0·37) and 1·42 (0·17) respectively (both p = NS) (fig 6).

No differences in intensity ratio were seen between angiographically documented reperfused and non-reperfused myocardial areas after Gd-DTPA. Before Gd-DTPA the intensity ratios were 1·16 (0·18) and 1·11 (0·15) respectively (p = NS), and after Gd-DTPA the intensity ratios were 1·51 (0·34) and 1·55 (0·17) respectively (p = NS) (fig 7).

Homogeneous contrast enhancement (type I) was seen in five (26%) of the 19 patients who showed reperfusion and in one (12·5%) of eight patients who did not show reperfusion, indicating that this criterion has a low sensitivity for reperfusion. Although there was inhomogeneous contrast enhancement (type II) in seven (87·5%) of eight patients without reperfusion, this was a non-specific phenomenon because it

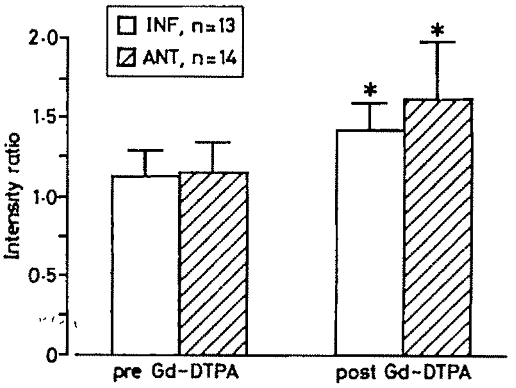

*Figure 6 Intensity ratio before and after Gd-DTPA administration in relation to infarct size (inferior versus anterior). There was no significant effect of infarct size on intensity ratio before or after Gd-DTPA administration. Within each group the intensity ratio increased significantly after Gd-DTPA administration (*p < 0·001).*

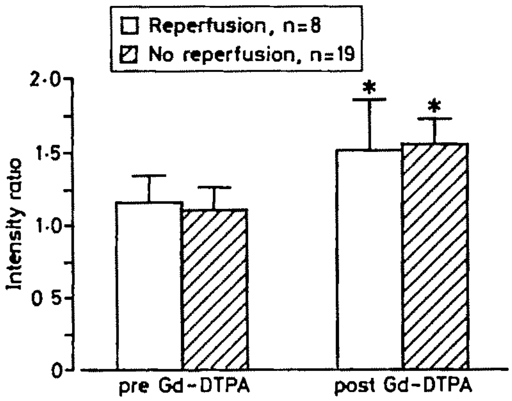

Figure 7 Intensity ratio before and after Gd-DTPA administration in relation to the effect of thrombolysis (reperfusion versus non-reperfusion). There was no significant effect of thrombolysis on intensity ratio before or after Gd-DTPA administration. Within each group the intensity ratio increased significantly after Gd-DTPA administration ($p < 0.001$).*

was also seen in 11 (56%) of 19 patients who showed reperfusion.

Discussion

This study extends our previous findings that the contrast agent Gd-DTPA significantly improves the detection of infarcted myocardium on T_1 weighted spin echo images.[12 16 20 21] The use of Gd-DTPA as a paramagnetic contrast agent for improving the potential of magnetic resonance imaging to assess coronary artery disease was thoroughly investigated in experimental studies[13–15]. Wesbey *et al* administered Gd-DTPA to dogs 20 minutes after coronary artery ligation.[13] Non-ischaemic zones from hearts in dogs injected with Gd-DTPA showed significantly shorter relaxation times than infarcted zones excised 90 seconds after the adminstration of Gd-DTPA. In contrast, five minutes after injection, infarcted myocardium showed shortened relaxation times while non-infarcted myocardium returned to normal values, suggesting early accumulation in and clearance from normal myocardium and delayed accumulation in and clearance from infarcted myocardium. Administration of Gd-DTPA considerably shortened T_1 relaxation time in the infarcted areas and so enhances the signal intensity in the infarcted myocardium. In our study, both visual inspection and measurement of signal intensities allowed clear delineation of infarcts on the post-contrast images. Our study also showed increased signal intensity after Gd-DTPA both in the infarcted and non-infarcted areas. These findings accord with those of Eichstaedt *et al* who used Gd-DTPA to investigate 26 patients after a sustained myocardial infarction.[10] Eleven patients were imaged 5–10 days after infarction (designated acute infarcts) and 15 patients were imaged later. Signal intensity within areas of acute infarction was increased by an average of 70% compared with the pre-contrast images, while the non-infarcted areas showed an average increase of 20% after Gd-DTPA. In the remaining 15 patients no significant contrast enhancement was seen after the administration of Gd-DTPA. Since in Eichstaedt *et al*'s study the minimum interval between the onset of infarction and magnetic resonance imaging was five days, it contains no data about the most acute phase of infarction.[10] In a preliminary study at our hospital, five patients underwent magnetic resonance imaging with Gd-DTPA 2–17 days after myocardial infarction.[13] The signal intensity ratio of infarcted versus normal myocardium was significantly greater after the administration of Gd-DTPA than before Gd-DTPA. Moreover, the use of Gd-DTPA improved infarct definition and obviated the need for the more time-consuming T_2-weighted imaging approach. These findings were confirmed in 17 patients with acute myocardial infarction who showed an average increase in signal intensity of 20% in normal areas and 45% in infarcted areas.[16 20] Maximal contrast was measured 15–25 minutes after the administration of Gd-DTPA.

A remarkable finding in the present study was the significant enhancement of signal intensity in the infarcted areas of the patients who were studied more than 72 hours after the acute event compared with the signal intensities of those patients who were studied earlier. This suggests greater delivery or slower wash-out of Gd-DTPA or both in a later stage of the infarction process. The supply of Gd-DTPA most probably depends on the extent of collateral circulation, neovascularisation, and on slow wash-out from the infarct zone caused by cellular damage. These histopathological processes occur later in the course of the healing process of the infarction and this may explain our findings of increased signal intensity at that time. Our data are supported by those of Rehr *et al* who showed improved detection with Gd-DTPA in experimental acute myocardial infarction; this effect was more prominent in dogs imaged after 4 or 5 days than in those imaged after 1 or 2 days.[14] Nishimura *et al* studied 12 patients with acute myocardial infarction by gated magnetic resonance imaging and Gd-DTPA at four different times (on average 5, 12, 30, and 90 days) after the acute onset.[23] The increase of signal intensity in the infarcted areas was 75%, 83%, 50%, and 17% respectively. The normal areas showed an average increase of 20% after Gd-DTPA on days 5 and 12.

We found no difference in signal intensity between small and large infarcted areas, based on a cut off point of 1000 U/l of α hydroxybutyrate dehydrogenase release. Because we used only a few slices per magnetic resonance imaging, an anatomical assessment of infarct size was not performed because the extent of infarction can only be assessed by a multislice imaging technique encompassing the whole left ventricle. We found no difference in signal intensity between anterior and inferior infarcts.

Magnetic resonance imaging with Gd-DTPA did not allow the non-invasive identification of patients with early reperfusion after thrombolytic treatment and those without because we were unable to show differences in signal intensity or in morphological appearance between reperfused and non-reperfused areas. Previous experimental data from McNamara *et al* had shown that Gd-DTPA significantly shortened T_1 in myocardial regions with irreversible injury, while no differences in signal intensity or relaxation times were seen in reversibly injured myocardium.[18] Peshock *et al* showed in dog hearts that contrast enhancement after Gd-DTPA was considerably augmented in reperfused myocardium with a uniform contrast pattern in reperfused hearts and a non-uniform contrast enhancement in non-reperfused hearts.[19] However, it is difficult to compare our clinical observations with those of earlier experimental studies.[17–19] Peshock *et al* performed magnetic resonance imaging immediately after controlled episodes of coronary artery ligation, which in some instances were followed by an hour of reperfusion.[19] In contrast, in our patients the mean interval between the onset of infarction and magnetic resonance imaging was 93 hours, and only one patient could be studied within 24 hours of acute coronary arteriography. At that time the infarct related arteries may be reoccluded and it is therefore not known whether or not the areas were reperfused during the imaging procedure. Unfortunately, we found it impracticable to study patients earlier after acute coronary arteriography.

The number of patients without reperfusion may have been too small for any differences between them and those who had early reperfusion to be statistically significant but it seems unlikely that a larger sample size would show clinically relevant differences. Been *et al* found no differences in T_1 values (without the use of Gd-DTPA) between patients with reperfusion and those without,[7] suggesting that alterations in T_1 are complex and do not reflect specific histological findings. Perhaps more accurate magnetic resonance imaging measurements of infarct size may be helpful in distinguishing between reperfused and non-reperfused myocardium,[24] but appropriate software programs have yet to be developed. Furthermore, determinations of infarct size from the cumulative release of α hydroxybutyrate dehydrogenase have clearly showed that, though the mean infarct size was smaller in patients with successful thrombolytic treatment, there was considerable overlap with patients in whom no recanalisation was achieved.[25] In the current study we found no significant difference in enzymatically determined infarct size.

Our study shows that Gd-DTPA improves the detection and localisation of infarct zones by magnetic resonance imaging by a T_1 weighted spin echo sequence in patients treated with thrombolysis for acute myocardial infarction, but is of little if any value in the non-invasive identification of patients in whom thrombolytic treatment was successful. Our finding that maximal contrast enhancement is achieved more than 72 hours after the onset of acute myocardial infarction is clinically relevant because this suggests that Gd-DTPA enhanced magnetic resonance imaging studies in patients with acute myocardial infarction should be delayed until they are beyond the critical phase of infarction.

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Monitoring the effect of heparin by measurement of activated clotting time during and after percutaneous transluminal coronary angioplasty

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Abstract

The anticoagulant effect of heparin during percutaneous transluminal coronary angioplasty was monitored by measurements of the activated clotting time in two studies that compared the effects of a single bolus of heparin with those of a bolus of heparin combined with a continuous infusion of the drug. In a preliminary study 40 patients received a single heparin bolus of 10 000 units (protocol I) and a further 40 patients received both a heparin bolus of 10 000 and a continuous infusion of heparin at a rate of 2000 units per hour (protocol II). During the first 45 minutes, nine patients (23%) in protocol I but only two patients (5%) in protocol II were found to be inadequately anticoagulated. For 24 hours after angioplasty both groups received an infusion of heparin at the rate of 2000 units per hour which led to consistent anticoagulation in 73 (91%) of patients. In a subsequent randomised study, 40 patients received heparin according to either protocol I or II. Protocol II was again found to lead to a higher rate of adequate anticoagulation. During the first 60 minutes 11 patients (55%) in protocol I but only three patients (15%) in protocol II were inadequately anticoagulated. In addition, the activated clotting time of arterial blood in the first 30 minutes was significantly higher than that of venous blood in 70% of the patients.

A bolus of heparin (10 000 units) together with an infusion of 2000 units per hour should be routinely given during coronary angioplasty. The effects of heparin, which can vary considerably from patient to patient, should be monitored by the measurement of the activated clotting time of arterial blood.

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Heparin is administered routinely during percutaneous transluminal coronary angioplasty[1] in order to prevent thrombus formation. Commonly, 10 000 units of heparin is given at the start of percutaneous transluminal coronary angioplasty and a further 5000 units is administered if the procedure lasts for more than one hour.[2] The effects of heparin, however, vary considerably from patient to patient[3] so that some may be at risk from inadequate anticoagulation.

The activated clotting time reflects heparin activity.[4] Activated clotting time can be rapidly and repeatedly measured in the catheterisation laboratory by an automated instrument. The purpose of this study was to investigate the value of measurement of activated clotting time during percutaneous transluminal coronary angioplasty and to attempt to develop a regimen of heparin administration that would provide consistently effective anticoagulation during the procedure.

Some recommend routine infusion of heparin for 24 hours after the procedure to prevent thrombus formation at the site of dilatation.[5] Others suggest that such infusion should be given only when the procedure is complicated by coronary artery dissection.[6] Many of the complications of percutaneous transluminal coronary angioplasty, including restenosis, are related to intravascular thrombus formation.[7,8] A subsidiary purpose of this study was to try to establish a suitable dosage regimen for continuous heparin infusion if indicated and also to see whether such a regimen had a pronounced effect on the rate of coronary restenosis.

Patients and methods

Two studies were carried out. In each study, patients received either a bolus injection of heparin or a bolus of heparin together with a continuous infusion.

PRELIMINARY STUDY

Observations were made in 80 consecutive patients undergoing percutaneous transluminal coronary angioplasty for stable or unstable angina (table).

The anticoagulant effect of heparin was monitored every 15 minutes during percutaneous transluminal coronary angioplasty by measurement of the activated clotting time by a

Patients' details

	Protocol I	*Protocol II*
Number of patients	60	60
Age (yr)	40–63 (mean 58)	43–68 (mean 54)
Sex		
Male	38	40
Female	22	20
Type of angina.		
Stable	42	48
Unstable	18	12

Hemochron blood coagulation timing system (International Technidyne Corporation, New Jersey, USA). Blood samples were collected from the angioplasty guiding catheter after aspiration of 6 ml of blood. Whole blood (2 ml) was placed in a Hemochron test tube containing 12 mg of Celite and a cylindrical bar magnet. The test tube was shaken vigorously ten times and was placed in the instrument's incubated test well, which has a magnet detector at its base. The temperature was maintained at 37°C by the incubator. The cylindrical bar magnet remained close to the detector as the tube slowly rotated. When a fibrin mass formed, its adhesion to the magnet and a plastic structure within the tube caused the magnet to rotate with the tube. The magnet was thereby displaced from its initial position adjacent to the detector. This activated the timer and an audible tone signalled this end point. The coagulation time was displayed in seconds.

The effective anticoagulation was defined as an activated clotting time of >250 s.

The first 40 patients received a single bolus of 10 000 units of heparin at the start of the procedure (protocol I). The bolus of heparin was administered through a sheath in the femoral artery which was then flushed with 10 ml of saline. The second group of 40 patients received 10 000 units of heparin as a bolus injection immediately followed by continuous infusion of heparin 2000 units per hour (protocol II). If the activated clotting time fell below 250 s an additional bolus of 5000 units of heparin was given.

For 24 hours after percutaneous transluminal coronary angioplasty had been completed both groups received a continuous infusion at a rate of 2000 units per hour. Activated clotting time was measured at intervals over 24 hours on at least four occasions.

RANDOMISED STUDY

In a subsequent study, a further 40 patients (table) were randomised to receive heparin according to either protocol I or II. In this study, the route of heparin administration was randomised so that the drug was given through a sheath in either the femoral vein or in the femoral artery. The anticoagulant effect of heparin was monitored every 15 minutes for 60 minutes. Samples were collected, after aspiration of 6 ml of blood, from both the guiding catheter in the aorta and the sheath in the femoral vein. Both the venous and arterial activated clotting time measurements were assessed simultaneously. A HemoTec (Colorado, USA) machine was used to facilitate simultaneous activated clotting time measurements of two blood samples.

Like the Hemochron machine, the HemoTec blood coagulation timing system also detected in vitro clot formation. One ml blood was collected in cartridges containing the reagent (0·1 ml of kaolin activator) and a plunger. The machine was operated by dropping the plunger through the test sample at programmed intervals. When clotting occurred, the clot retarded the fall of the plunger and this was detected photo-optically. An audible tone signalled the end point.

To assess the variability in activated clotting time measurements, duplicate samples were obtained five minutes apart from 10 other patients. The samples were analysed by a single operator (five patients) and two operators (five patients) using the Hemochron machine.

Results

PRELIMINARY STUDY

Activated clotting time values (protocol I and II)

Of those patients receiving heparin according to protocol I, six, two, and one patients were inadequately anticoagulated at 15, 30, and 45 minutes, respectively. Whereas only two patients were inadequately anticoagulated by protocol I (at 30 and 45 minutes). Thus nine (23%) patients in protocol I and two (5%) patients in protocol II were inadequately anticoagulated and required further doses of heparin.

Activated clotting time values during continuous heparin infusion after angioplasty

During the continuous intravenous heparin infusion after completion of percutaneous transluminal coronary angioplasty, most patients achieved a steady activated clotting time value; however, seven (9%) patients were inadequately anticoagulated. Their heparin dosage was not altered. The incidence of restenosis in those who were adequately anticoagulated was 28%, similar to our previous 80 consecutive patients undergoing angioplasty and to restenosis rates reported in many other reports.

RANDOMISED STUDY

Activated clotting time values (protocol I and II)

Figures 1 and 2 show the activated clotting time values in arterial blood of patients receiving heparin according to protocols I and II. In patients receiving heparin according to protocol I, three, one, two, and five patients were inadequately anticoagulated at 15, 30, 45, and 60 minutes, respectively. Whereas in

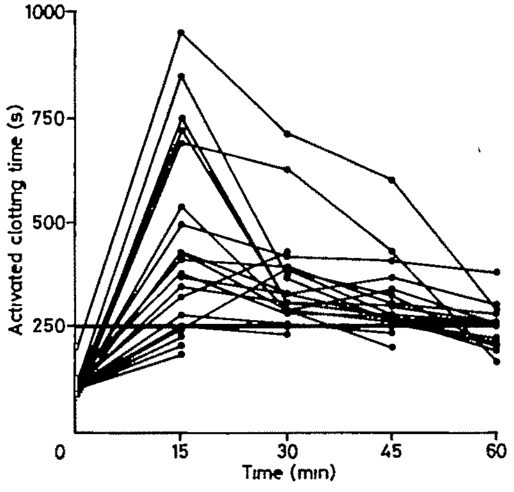

Figure 1 Activated clotting time in patients receiving a single bolus of 10 000 units of heparin at the start of the procedure (randomised study).

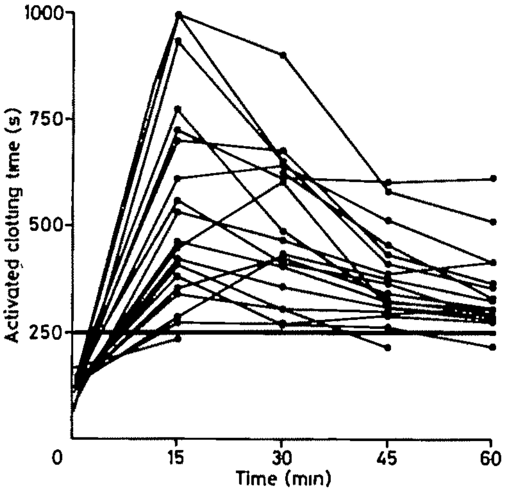

Figure 2 Activated clotting time in patients receiving 10 000 units heparin as a bolus followed by continuous infusion of 2000 units per hour (randomised study).

protocol II, three patients were inadequately anticoagulated at 15, 45, and 60 minutes. Thus 11 (55%) patients in protocol I and three (15%) patients in protocol II required additional doses of heparin.

Arteriovenous activated clotting time difference
Figure 3 shows the mean arterial and venous activated clotting time values measured every 15 minutes in the 40 patients who were randomised to protocol I and II. In 28 patients (70%) the arterial activated clotting time values were markedly higher during the first 30 minutes.

Complications
Several patients bled slightly around the sheath in the femoral artery during the 24 hour heparin infusion but did not require any therapeutic intervention. One patient bled profusely from around the arterial sheath during continuous heparin infusion and required blood transfusion. Her activated clotting time varied from 250 to 300 s.

Factors affecting heparin activity
Body weight, surface area, age, and sex did not affect the level of anticoagulation.

Variability
The variability in activated clotting time measurement was <8% when two duplicate samples were analysed by a single operator and <10% when they were analysed by two operators.

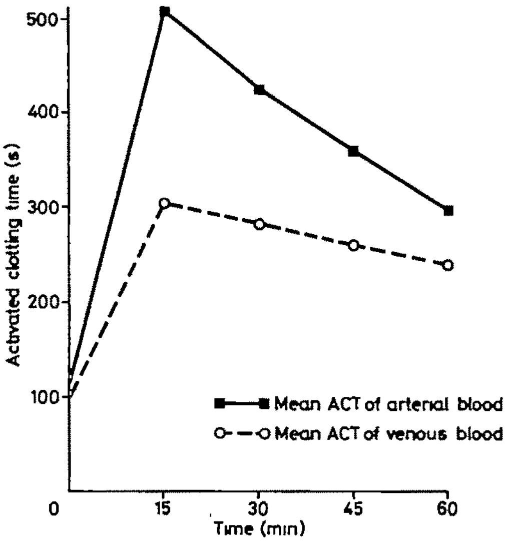

Figure 3 Activated clotting time in arterial and venous blood.

Discussion

Before we started the present study two of our patients had developed acute coronary occlusion during angioplasty of the left anterior descending artery and both had to undergo urgent coronary artery bypass surgery. Thrombi were found not only at the site of balloon inflation but also in the left circumflex artery. Both the patients had received 10 000 units of heparin but were found to be inadequately anticoagulated (activated clotting time <200 s). This led us to monitor heparin induced systemic anticoagulation during angioplasty.

Heparin binds to circulating antithrombin III. The resulting complex inhibits thrombin and other coagulation factors. Heparin prevents thrombin from inducing platelet aggregation and is also believed to have a fibrinolytic action.[9]

The mean half life of heparin activity has been reported as being between 60 and 90 minutes.[10 11] In 1975, Bull *et al* using manual measurement of activated clotting time reported that the individual sensitivity to heparin varied threefold and heparin half life varied fourfold.[3] Our results confirm the wide variation in sensitivity to heparin and in the duration of effective anticoagulation. This may be because of individual differences in heparin clearance or variations in concentrations of circulating coagulation factors such as antithrombin III, platelet factor 4, and heparin neutralising proteins.

It is common practice to give 10 000 units of heparin before percutaneous transluminal coronary angioplasty and a further 5000 units if the procedure extends beyond one hour.[2] Heparin administered according to this protocol, however, will leave a significant number of patients inadequately anticoagulated, exposing them to the risk of thrombotic complications. One study has shown that 73% of coronary artery occlusions were related to ineffective anticoagulation.[12] Hollman *et al* reported that 85% of acute occlusions occurred at the time of diminishing anticoagulation.[2] Though both studies refer to acute occlusion after leaving the catheter laboratory, the results show the importance of adequate anticoagulation.

Our results show that to maintain effective anticoagulation during percutaneous transluminal coronary angioplasty, systemic anticoagulation induced by heparin should be monitored. There is controversy about the optimal in vitro test for monitoring heparin treatment. The consensus is that the degree of prolongation of anticoagulation effect gives a better assessment than heparin concentration, because the heparin effect reflects the balance between the direct action of the drug on clotting factors and the ability of other substances to potentiate or antagonise it.

The tests that are commonly used are whole blood clotting time, activated clotting time, and activated partial thromboplastin time. Each test has its drawbacks. Whole blood clotting time is time consuming and there is lack of reproducible results.[13] Activated partial thromboplastin time is a popular laboratory test and is considered to be sensitive but it is time consuming and cannot be easily performed in the catheterisation laboratory. Furthermore, its relation to the heparin concentration is linear only over a small heparin dosage range.[14] The result also varies according to the reagent and instrument used.[15]

We found the automated activated clotting time (Haemochron and HemoTec) tests simple, inexpensive, and easy to use. They gave reproducible results. Tests performed on whole blood have two advantages. They can be performed quickly and they reflect the antiheparin activity of the platelets. Both produced results rapidly enough for the titration of heparin in the catheterisation laboratory or coronary care unit.

Bull *et al* recommended that the activated clotting time during cardiopulmonary bypass should be maintained at >300 s to avoid clot formation.[3] Young *et al* reported that activated clotting time should be maintained at >400 s to prevent microemboli in the extracorporeal circulation.[16] Schriever *et al* found that the activated clotting time gave a strong linear correlation with blood heparin concentration unlike the activated partial thromboplastin time. They concluded that an activated clotting time value between 1·6 and 2·2 times baseline provides effective anticoagulation.[17] We arbitrarily chose to maintain our patients' activated clotting time at >250 s, which was >2·5 times the baseline in most patients. We chose this value because we thought that patients undergoing percutaneous transluminal coronary angioplasty require less heparin than patients on cardiopulmonary bypass but they need sufficient heparin to prevent thromboembolism.

Heparin, in addition to preventing thrombus formation, inhibits platelet to platelet interaction and has also been shown experimentally to suppress the smooth cell proliferation, which contributes to the phenomenon of restenosis.[18] We continued heparin infusion for 24 hours after percutaneous transluminal coronary angioplasty to assess its effect on restenosis. The results showed no significant reduction in the incidence of restenosis in the patients who were adequately anticoagulated compared with our previous 80 consecutive patients undergoing angioplasty or compared with reported rates of restenosis.

In the subsequent study we found that the activated clotting time values of arterial blood were considerably higher than those of venous blood. We do not think that intermittent flushing of the arterial line with saline containing a very small amount of heparin (approximately 30–40 ml saline containing <200 units of heparin) explains the difference. The differences may be either related to heparin metabolism or possibly to the anticoagulant effect of the contrast media. Our present knowledge of heparin metabolism is insufficient and further studies are necessary to explain the discrepancy. We recommend activated clotting time monitoring of the arterial blood collected from the guiding catheter because this is more likely to reflect the level of anticoagulation at the site of angioplasty.

Heparin is obtained commercially from porcine intestinal mucosa or bovine lungs. The activities of these two preparations are identical.[19] We used heparin obtained from porcine intestinal mucosa.

We conclude that a bolus of 10 000 units of heparin together with an infusion of 2000 units per hour resulted in adequate anticoagulation in most patients. Activated clotting time should be monitored in all patients to identify those who may be at higher risk of thromboembolic complications because of inadequate anticoagulation. Arterial values of activated clotting time are likely to be higher than venous measurements. A large study is necessary to validate the clinical effectiveness of adequate heparin anticoagulation.

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Effects of food on the central and peripheral haemodynamic response to upright exercise in normal volunteers

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Abstract

The central and peripheral haemodynamic effects of a modest meal were investigated in healthy volunteers at rest and in response to submaximal exercise. The meal increased heart rate, cardiac output, oxygen consumption, carbon dioxide production, and minute ventilation at rest and during exercise. The effects of food were additive to those induced by the exercise. Food had no effect on limb blood flow and lowered total systemic vascular resistance suggesting that there were no compensatory changes in regional blood flow to help redirect blood to the gut.

An increase in cardiac output, and therefore myocardial work, is the predominant cardiovascular response to eating and this may help explain the postprandial deterioration in symptoms of some patients with cardiovascular disorders.

The distribution of cardiac output to the main vascular beds of humans is unequal; at rest 25% is delivered to the splanchnic bed, 20% to skeletal muscle and the kidneys, 12% to the brain, 9% to the skin, and 4% to the heart.[1] The increased demand of metabolically active tissue in response to emotional or physical stress can be met by an increase in cardiac output, a redirection of regional blood flow, or by both these mechanisms. The changes in regional blood flow are likely to be complex but are often predictable. In response to upright exercise cardiac output increases to augment blood flow to the exercising skeletal muscle of the calf and blood is redirected away from the non-exercising forearm further to help this increase in calf blood flow.[2] Knowledge of these complex changes is important for our understanding of how exercise may aggravate the symptoms of patients with cardiovascular disease.

Eating is another common but less well recognised cause of stress. The first report that food increases cardiac output came in 1929[3] but it was surprisingly difficult to reproduce this observation.[4–6] Intuitively, you might expect that the increased requirement for gut blood flow after a meal would be partly met by an increase in cardiac output and partly by a redistribution of blood flow from other vascular beds, but surprisingly little is known about the changes in regional blood flow after food.

Because eating can also worsen the symptoms of patients with certain cardiovascular diseases, particularly angina, it is important to examine its effects on cardiac output and regional blood flow in association with exercise.

Patients and methods

VOLUNTEERS

Ten (eight men) healthy volunteers took part in the study. They were aged 20–41 years. All denied any symptoms suggestive of cardiovascular disease and all had a normal physical examination. All gave informed consent and the study fulfilled the requirements of the local ethics committee.

METHODS

All measurements were carried out in a temperature controlled room of 24–25°C. The volunteers were familiarised with the experimental techniques on at least one occasion before the study.

They fasted from 12 midnight the day before the study. All rested in the laboratory for at least 30 minutes on the morning of the study before cardiac output and limb blood flow at rest were measured. The exercise test was then performed and cardiac output and oxygen consumption were measured. Immediately after the end of exercise measurements of limb blood flow were repeated.

Thirty minutes after the first exercise test the volunteers were given a standard meal of 1400 kcal (5·88 MJ) and 30 minutes after this the measurements of cardiac output and limb blood flow at rest were repeated. We have previously shown that 60 minutes' rest is sufficient time for values to return to normal.[7] Volunteers then performed a second exercise test with measurements being made in the same way as in the first test.

EXERCISE TESTING

This was performed with a modified Bruce protocol. The speed and slope of the treadmill were increased after three minutes of stages II and IV and four minutes of the other stages to allow sufficient time for cardiac output to be measured.

Stage	I	II	III	IV	V
Speed (km/h)	2·7	2·7	2·7	2·7	4·0
Slope°	0	1·3	2·6	4·3	5·4

An electrocardiogram was monitored continuously and arterial blood pressure was measured at rest and during exercise with a

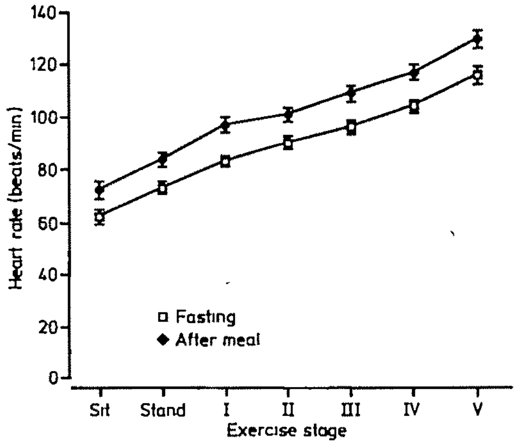

Figure 1 Mean (SEM) values of heart rate at rest and during exercise in fasting volunteers and after the meal ($p < 0\cdot0001$)

sphygmomanometer (diastolic pressure taken at phase V).

MEASUREMENTS OF CARDIAC OUTPUT

Cardiac output was measured by the indirect Fick principle with carbon dioxide.[5] Gas analysis was made with a mass spectrometer (VG Medical Systems). Carbon dioxide production was calculated from minute ventilation and mixed expired carbon dioxide concentration. Pulmonary venous carbon dioxide partial pressure (that is systemic arterial carbon dioxide partial pressure) was derived from end tidal carbon dioxide partial pressure, and mixed venous carbon dioxide partial pressure was estimated from a rebreathing manoeuvre. Volunteers hyperventilated into an anaesthetic bag containing a mixture of oxygen and 8–10% carbon dioxide. When a carbon dioxide concentration, measured at the mouth, reached a plateau there was no net exchange of carbon dioxide across the lungs and this plateau value is related to mixed venous carbon dioxide partial pressure. These variables can then be used in the Fick equation to calculate cardiac output. Cardiac output was measured sitting and standing and at the end of stages I, III, and V of the treadmill protocol. Systemic vascular resistance was calculated by dividing mean arterial blood pressure (2/3 diastolic + 1/3 systolic) by cardiac output.

MEASUREMENT OF OXYGEN CONSUMPTION

Systemic oxygen consumption was calculated from minute ventilation and the difference between mixed expired oxygen concentration and atmospheric oxygen. Measurements were made at the same times as cardiac output.

MEASUREMENT OF LIMB BLOOD FLOW

Forearm and calf blood flow were measured simultaneously by venous occlusion plethysmography with mercury in silastic strain gauges.[8] Measurements were made at rest before each exercise test and from 3–13 minutes after the end of each test.[7]

STATISTICAL ANALYSIS

This was performed by analysis of variance for repeated measures.

Results

HEART RATE AND BLOOD PRESSURE

Figure 1 shows the effects of the meal on mean (SEM) values of heart rate at rest and during exercise. The meal increased heart rate measured with the volunteers sitting from 62 (2·76) to 72 (3·31) beats/minute and this level of increase was maintained throughout exercise ($p < 0\cdot0001$). At the end of stage V the preprandial heart rate was 116 (3·40) compared with a value of 130 (3·42) beats/minute after the meal.

Figure 2 shows the effect of food on mean (SEM) values of systolic and diastolic blood pressure at rest and during exercise. There was a trend to a greater increase in systolic blood pressure during exercise and a fall in diastolic pressure, but neither of these reached statistical significance ($p = 0\cdot1442$ for systolic pressure and $p = 0\cdot1169$ for diastolic blood pressure).

CARDIAC OUTPUT

Figure 3 shows the effect of food on cardiac output at rest and on the changes in cardiac output induced by exercise. Cardiac output measured when the volunteers were sitting increased from a mean (SEM) fasting value of 4·45 (0·18) to 5·72 (0·22) l/min after the meal and at the end of stage V the fasting value was 12·70 (0·60) compared with a postprandial value of 14·10 (0·64) l/min ($p < 0\cdot0001$).

OXYGEN CONSUMPTION, CARBON DIOXIDE PRODUCTION, AND MINUTE VENTILATION

Figure 4a shows the mean (SEM) values of systemic oxygen consumption at rest and during exercise before and after the meal. Oxygen consumption in the volunteers sitting was 3·52 (0·15) ml/kg/minute and increased to 18·06 (0 69) ml/kg/minute at stage V of the protocol with the subjects fasting. After the

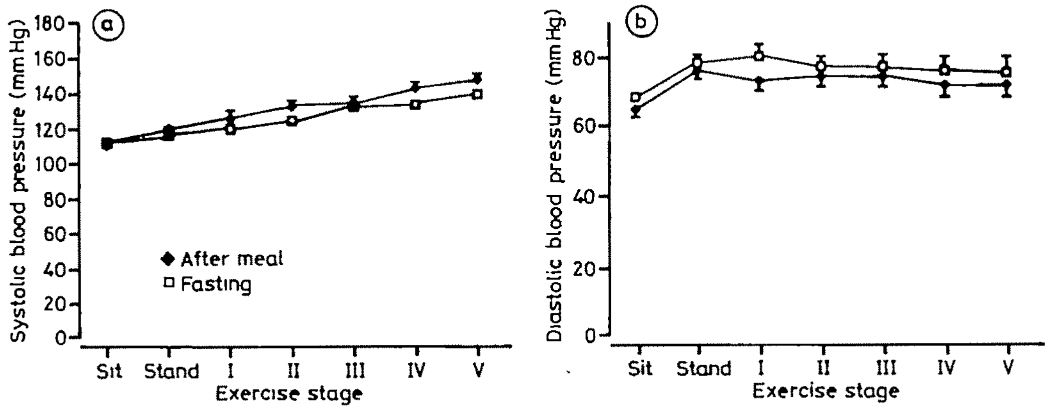

Figure 2 Mean (SEM) values of (a) systolic and (b) diastolic blood pressure at rest and during exercise in fasting volunteers and after the meal ($p = 0\cdot1442$ for systolic and $p = 0\ 1169$ for diastolic pressure).

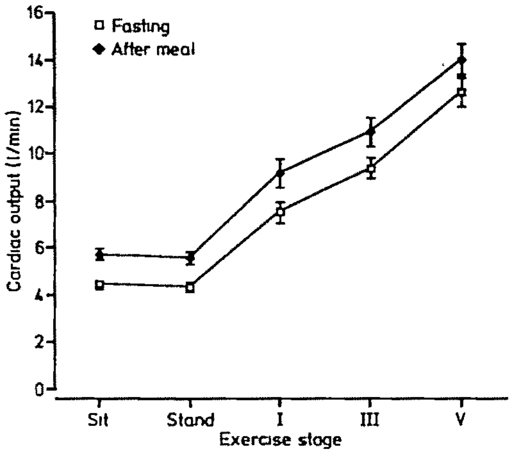

Figure 3 Mean (SEM) values of cardiac output at rest and during exercise in fasting volunteers and after the meal ($p < 0.0001$).

meal oxygen consumption increased significantly ($p = 0.0041$); the value when sitting was 4·48 (0·26) ml/kg/minute increasing to 18·84 (0·59) ml/kg/minute at stage V of the exercise protocol.

In association with this, carbon dioxide production was also increased postprandially ($p < 0.001$). The mean value before the meal in sitting volunteers was 2·93 (0·31) ml/kg/min; this increased to 15·91 ml/kg/min at stage V of the protocol and after the meal the sitting value had increased to 4·04 (0·25) and the value at stage V of the exercise protocol to 17·59 (0·50) ml/kg/min.

Figure 4b shows that the meal increased minute ventilation at rest and during exercise ($p = 0.0002$). Mean values of minute ventilation at rest and during stage V of the protocol increased from 6·51 (0·40) and 23·69 (1·07) l/min preprandially to 8·61 (0·43) and 26·82 (1·0) l/min after food.

LIMB BLOOD FLOW

Figure 5 shows the changes in forearm and calf blood flow at rest and 3–13 minutes after exercise. Exercise caused the expected increase in calf blood flow and decrease in forearm blood flow. Resting limb blood flow was increased by food—in the calf from 3·34 (0·48) to 3·71 (0·37) ml/100 ml/minute and in the forearm from 2·97 (0·24) to 3·38 (0·23) ml/100 ml/min. Although the meal had no significant effect on blood flow after exercise ($p = 0.22$ for calf and $p = 0.20$ for forearm) it was always slightly higher postprandially.

SYSTEMIC VASCULAR RESISTANCE

Figure 6 shows the changes in systemic vascular resistance at rest and during exercise. Mean systemic vascular resistance in the volunteers when sitting was lower after a meal (14·09 (0·41) units) than when the volunteers were fasting (18·79 (0·55) units). Throughout exercise total systemic vascular resistance was also lower after eating ($p < 0.001$).

Discussion

We found that a modest meal had considerable effects on the circulation and on the metabolic requirements of the body as measured by respiratory gas exchange. Furthermore, in response to exercise these changes persist and are additional to those produced by exercise. The changes are likely to be interrelated and may help to explain why some cardiovascular diseases are aggravated by eating.

The digestion and absorption of food is a metabolically active process that requires an increased delivery of oxygen to the gut. Eating a meal is undoubtedly associated with a higher

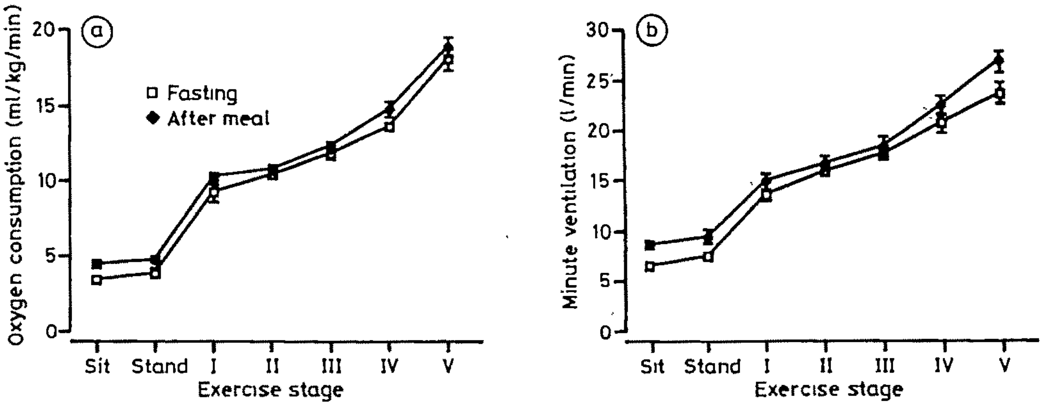

Figure 4 (a) Mean (SEM) values of systemic oxygen consumption at rest and during exercise in fasting volunteers and after the meal ($p = 0.0041$). (b) Mean (SEM) values of minute ventilation at rest and during exercise in fasting volunteers and after the meal ($p = 0.0002$).

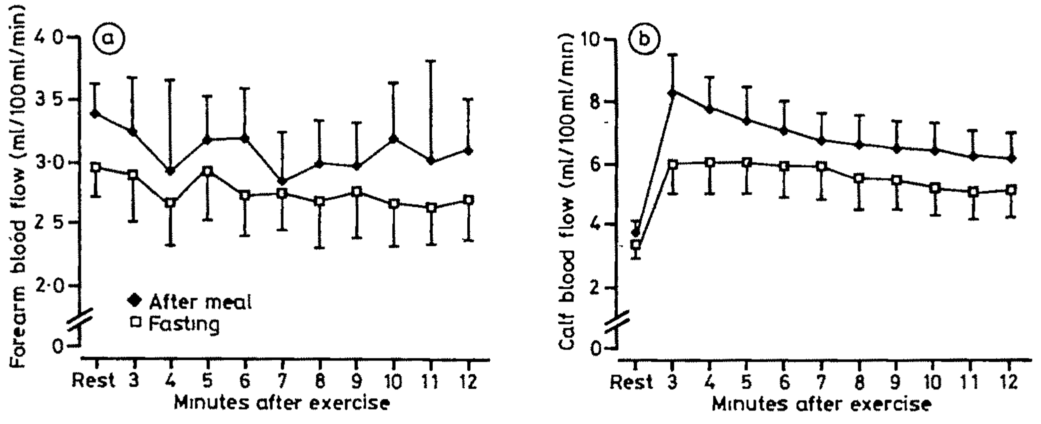

Figure 5 Mean (SEM) values of (a) forearm and (b) calf blood flow at rest and 3–13 minutes after exercise in fasting volunteers and after the meal ($p = 0.20$ for forearm and $p = 0.22$ for calf blood flow).

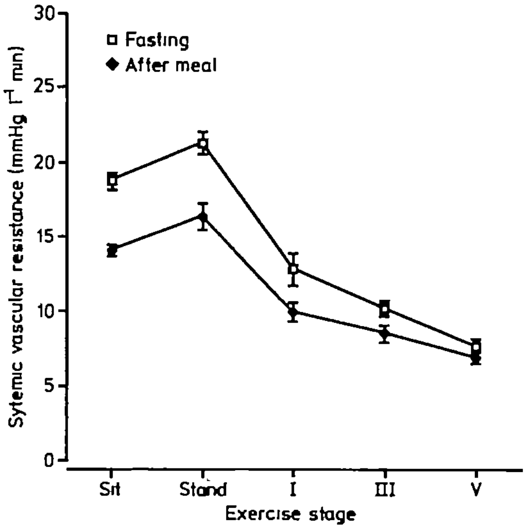

Figure 6 Mean (SEM) values for systemic vascular resistance at rest and during exercise in fasting volunteers and after the meal ($p < 0.001$).

blood flow to the gut[9] but precisely how this is achieved is not clear. Cardiac output could increase or blood flow could be directed away from other vascular beds. In this study, resting cardiac output increased but this was not accompanied by a reduction in blood flow to the limbs. Also, because total systemic vascular resistance fell it is unlikely that blood was directed away from other vascular beds by local vasoconstriction. Therefore, the increased blood flow requirement of the gut after food is met at rest by an increase in cardiac output and there is no evidence of redirection of blood flow from other vascular beds.

The changes during exercise are, surprisingly, similar and suggest that the cardiovascular effects of food are additive to those of exercise. We might have expected that the demand of exercising skeletal muscle would have been greater than that of the gut and that the increased blood flow to the gut after food would have been reduced during exercise to enhance delivery of blood to the calf. But this redirection did not occur, at least during submaximal exercise, and this imposes a greater workload on the myocardium to maintain a higher cardiac output.

The mechanism responsible for these changes is not absolutely clear. It has been suggested that they may be caused by increased activity of the sympathetic nervous system[10] and this would certainly fit with the changes in blood pressure and heart rate that we and others have reported.[11] Whatever the mechanism eating is a stressful activity and monitoring of respiratory gases indicates that it imposes an increased metabolic demand on the body. The increased oxygen consumption we have shown is not inconsiderable and matches the changes in cardiac output. The greater carbon dioxide production and minute ventilation also corresponds to the haemodynamic changes and this implies that the metabolic demands of the gut in response to food are the cause of the cardiovascular changes.

In view of the changes we have described it is surprising that more patients with cardiovascular diseases such as angina or heart failure, whose symptoms are caused either by increased myocardial work or a limited ability to increase cardiac output, do not describe a deterioration of their symptoms after a meal.

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Short term haemodynamic effects of converting enzyme inhibition before and after eating in patients with moderate heart failure caused by dilated cardiomyopathy: a double blind study

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Abstract

The haemodynamic changes that follow a meal can mimic the response to a vasodilator drug. To avoid overestimating the beneficial effects of treatment in uncontrolled studies, measurements of haemodynamic function are usually performed with patients in the fasting postabsorptive state. But such recordings are not representative of the resting patient during daily life. In this double blind placebo controlled study the short term haemodynamic effects of enalapril were assessed during 12 hours in 19 patients with moderate heart failure caused by dilated cardiomyopathy. The patients ate lunch and dinner and were studied in the absorptive and postabsorptive phases. In the placebo group systemic vascular resistance, mean arterial pressure, and the rate-pressure product fell significantly (5–16%) after lunch. Four hours after lunch the haemodynamic function had returned to baseline—that is the postabsorptive state. Enalapril, accentuated the haemodynamic effects during the absorptive state producing a larger post-prandial fall in mean arterial blood pressure and rate-pressure product and changes in the absorptive phase were maintained into the postabsorptive phase. Pulmonary wedge pressure fell significantly after treatment with enalapril. These overall changes during the study period indicated that enalapril reduced the preload and afterload on the heart—over and above the reduction produced by eating.

These findings suggest that the effects of enalapril given at rest to patients with moderate heart failure unload the heart and enhance the reduction of afterload induced by meals.

The haemodynamic effects of drugs are usually studied in fasting patients. Such recordings do not represent the effects in resting patients who are eating normally. Splanchnic vasodilatation in the absorptive phase may change central haemodynamic function[1–3] by reducing the systemic afterload.

Activation of the renin-angiotensin system, which increases systemic vascular resistance,[4] is an important compensatory mechanism in treated heart failure. Angiotensin-converting enzyme inhibitors cause systemic vasodilatation and reduce the load on the heart.[5 6] In heart failure such drugs may enhance the haemodynamic effects seen in the absorptive phase.

We investigated the complex haemodynamic effects of enalapril and eating and absorption in a double blind, controlled, randomised study in a homogeneous group of patients with treated moderate heart failure caused by dilated cardiomyopathy. We studied the angiotensin-converting enzyme inhibitor, enalapril, because its bioavailability was reported not to be influenced by food intake[7] and because a single oral dose gives therapeutic serum concentrations throughout a 12 hour study period.

Patients and methods

PATIENTS

We studied 19 patients (16 men and three women (41–62 years old (mean (SD)) 51 (6) years)), with moderate heart failure caused by dilated cardiomyopathy, which was treated with digoxin and frusemide. None of the patients had oedema and all had been clinically stable for at least two weeks. Inclusion criteria were an echocardiographically determined left ventricular end diastolic dimension of >30 mm/m^2, a left ventricular shortening fraction of $<20\%$, and an exercise capacity of > stage III and < stage IX according to a revised Naughton protocol.[8] We excluded patients with primary valve disease, suspected ischaemic heart disease, or congenital valve disease; those taking concomitant vasodilating agents; and those with right sided heart failure caused by pulmonary disease. The study protocol was approved by the local ethics committee. All patients gave their informed consent before entering the study.

PROTOCOL

The patient was admitted to hospital and served meals containing a known concentration of sodium. The daily doses of digoxin and frusemide remained unchanged. On the first day the blood volume was determined and echocardiography, a chest *x* ray, and an exercise test were performed. Serum albumin labelled with iodine-131 was used to measure the total blood volume.

Echocardiography was performed on patients in the left lateral position (ATL Mark III, 13 mm and 3 MHz transducer). The transducer position and cardiographic gain were adjusted to obtain optimal recordings of left ventricular dimensions in the short axis. We measured the left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD).[9] The mean value for five consecutive beats was calculated. The left ventricular shortening fraction was derived from the difference between LVEDD and LVESD divided by LVEDD.

Cardiac volume was measured radiologically by Jonsell's method.[10] Patients performed the exercise test sitting on an electrically braked ergometer. The load was increased every two minutes according to a modified Naughton protocol[8]:

Stage	I	II	III	IV	V	VI	VII	VIII	IX
W		10	20	30	50	70	90	110	130	150

The patients exercised until limiting symptoms developed—that is dyspnoea or fatigue or both.

On the third day at 5.30 am the patient was given a light breakfast and his or her daily dose of digoxin and frusemide. The right ventricle was catheterised at 8 am. A triple lumen balloon tipped thermodilution catheter (Edwards Laboratory, USA) was introduced via an antecubital or femoral vein under fluoroscopic guidance and was used to measure the right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. A polyethylene arterial catheter was introduced into the brachial or femoral artery to measure systemic pressure. The patient was placed in bed and transported to the coronary care unit for haemodynamic monitoring for 12 hours after two hours of rest. We used Hewlett-Packard transducers (HP 1290) and a Hewlett-Packard patient monitoring system (Model HP 78342A). All haemodynamic measurements were done by the same physician (BH). The measurements of haemodynamic function were made with the zero reference level at the midaxillary line with the patient supine and the bed in a horizontal position. Before each haemodynamic measurement we checked that the zero transducer pressure was the same as atmospheric pressure; calibration scales were displayed electronically. Cardiac output was measured by a bedside cardiac output computer (Cardiac Computer, Edwards Laboratories, model 9520) with the use of an iced injectate. Heart rate was derived from a continuously recorded electrocardiogram. The patients were randomised double blindly to enalapril 10 mg or placebo, and drugs were given at 0 hours. Recordings were made at 0, 1, 2, 3, 4, 5, 6, 8, and 12 hours. The patients ate portions of meals of their own choice after one and five hours. Snacks and coffee or tea were not allowed but water was available.

Serum concentrations of enalaprilat were measured by radioimmunoassay.[11]

ANALYSES

Mean right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), mean pulmonary capillary wedge pressure (PCWP), systolic systemic arterial pressure (SAP), and mean systemic arterial pressure (MAP) were measured by electronic integration. The mean of at least six determinations was calculated; each was the average for 12 seconds. Cardiac output (CO) was determined in triplicate. Heart rate (HR) was determined for one minute. Derived haemodynamic variables were calculated as follows:

$$\text{Cardiac index (CI) (l/min/m}^2\text{)} = \text{CO/body surface area}$$

$$\text{Stroke volume index (SVI) (ml/beat/m}^2\text{)} = \text{CI/HR}$$

$$\text{Systemic vascular resistance (SVR) (dyn.s.cm}^{-5}\text{)} = 80 \times \text{(MAP-RAP)/CO}$$

$$\text{Pulmonary vascular resistance (PVR) (dyn.s.cm}^{-5}\text{)} = 80 \times \text{(MPAP-PCWP)/CO}$$

$$\text{Rate-pressure product (RPP) (beats.mm Hg min)} = \text{HR} \times \text{SAP}$$

STATISTICAL ANALYSIS

Values are given as means (SD). Unpaired t tests were used to evaluate differences between two groups. Multiple comparisons of repeated measurements were tested by analysis of variance and Fisher's protected least square significance test. A p value of $<0{\cdot}05$ was regarded as significant.

Results

Ten patients were randomly allocated to enalapril and nine to placebo. One patient became symptomatically hypotensive six hours after administration of enalapril and was successfully treated with an infusion of saline. This patient was excluded from further study. The remaining 18 patients completed the study without complications.

Table 1 shows the clinical characteristics and non-invasive findings. The mean heart volume and the daily dose of frusemide were significantly larger in the group receiving enalapril than in the placebo group ($p < 0{\cdot}05$). Other characteristics were similar in the two groups. All patients had concentrations of serum sodium within the normal range.

There were no significant differences in haemodynamic variables between the two groups at baseline (0 hour, table 2).

Table 1 Clinical characteristics, non-invasive findings, blood volume, and serum sodium

	Placebo group (n = 9)		*Enalapril group (n = 9)*		*p value*
Age (yr)	53	(3)	50	(7)	NS
Sex (F/M)	2/7		1/8		NS
Duration of symptoms (mnth)	21	(12)	41	(30)	NS
Frusemide dosage (mg/day)	98	(45)	158	(65)	<0·05
ECG (AF/SR)	2/7		3/6		NS
Exercise duration (s)	701	(93)	692	(173)	NS
Chest *x* ray, heart volume (ml/m²)	712	(144)	872	(168)	<0·05
Echocardiography					
LVEDD (mm/m²)	37	(5)	39	(3)	NS
FS (%)	11	(4)	11	(3)	NS
Blood volume (l)	5·8	(1·4)	6·3	(1·3)	NS
Serum sodium (mmol/l)	140	(2)	142	(2)	NS

AF, atrial fibrillation; FS, left ventricular fractional shortening; LVEDD, left ventricular end diastolic diameter, SR, sinus rhythm

Table 2 Haemodynamic measurements (mean (SD)) in the placebo and enalapril groups

	Placebo group							
	Baseline		*Absorptive phase*				*Postabsorptive phase*	
	0 h		*2 h*		*3 h*		*5 h*	
HR	82	(14)	81	(11)	82	(8)	83	(12)
RAP	4	(3)	5	(3)	5	(4)	5	(4)*
MPAP	20	(8)	19	(6)	19	(5)	21	(8)
PCWP	11	(8)	10	(7)	10	(6)	12	(8)
MAP	85	(9)	81	(9)*	80	(12)*	84	(10)
CI	2·5	(0·5)	2·8	(0·5)**	2·7	(0·6)*	2·5	(0·6)
SVI	31	(8)	35	(8)***	33	(9)	30	(9)
SVR	1402	(308)	1176	(245)***	1194	(230)***	1371	(268)
PVR	159	(37)	144	(38)	136	(46)**	158	(53)
RPP	9422	(1729)	8914	(1567)*	8915	(1605)*	9227	(1621)

Statistical differences within groups compared with baseline are indicated as $^{*}p < 0·05$, $^{**}p < 0·01$, $^{***}p < 0·001$
Statistical differences in changes from baseline between groups are indicated as $^{†}p < 0·05$, $^{††}p < 0·01$.
HR, heart rate (beats/min); RAP, right atrial pressure (mm Hg), MPAP, mean pulmonary artery pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg), MAP, mean arterial pressure (mm Hg); CI, cardiac index (l/min/m^2), SVI, stroke volume index (ml/m^2), SVR, systemic vascular resistance (dyn.s cm^{-5}), PVR, pulmonary vascular resistance (dyn.s.cm^{-5}), RPP, rate-pressure product (beats. mm Hg/min)

HAEMODYNAMIC FUNCTION BEFORE AND AFTER MEALS IN THE PLACEBO GROUP

After the first meal (lunch), haemodynamic changes were greatest two and three hours after the start of the study (one and two hours after the meal) (table 2). Two hours after the start of the study (one hour after the meal, fig 1) mean arterial pressure (−5 (4)%, $p < 0·05$), systemic vascular resistance (−16 (9)%, $p < 0·001$), and the rate-pressure product (−5 (6)%, $p < 0·05$) were lower while the cardiac and stroke volume indices were higher (12 (8)%, $p < 0·01$ and 13 (7)%, $p < 0·001$, respectively). Heart rate, right atrial pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure were unchanged. These values returned to baseline five hours after the start of the study (four hours after the first meal); this indicated the start of the postabsorptive phase (fig 2). The changes after the second meal (dinner) were similar to those after the first one.

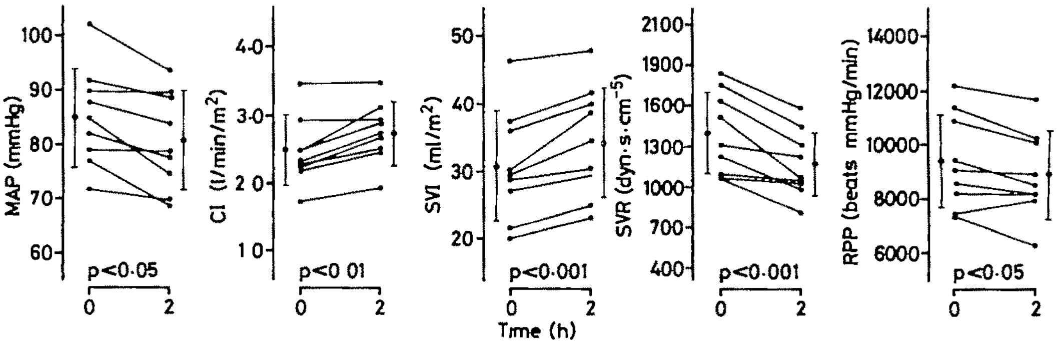
Fluctuations in haemodynamic variables not associated with eating were assessed by comparing estimates from postabsorptive determinations—that is at baseline and after five and 12 hours (fig 3). Compared with baseline values, right atrial pressure was increased after five hours while, in addition, after 12 hours heart rate, mean pulmonary artery and pulmonary capillary wedge pressures, cardiac index, and rate pressure product were also increased.

HAEMODYNAMIC FUNCTION IN THE ENALAPRIL GROUP

Serum concentrations of enalaprilat rose after only two hours (20·4 (9·8) ng/ml) (fig 4). Although the concentration was highest after four hours (27·9 (8·2) ng/ml), the difference between two and five hours was not statistically significant. After five hours the serum concentrations fell, reaching 11·7 (7·0) ng/ml after 12 hours. In the absorptive phase, after two and three hours, the changes in haemodynamic function resembled those in the placebo group. Compared with baseline values the mean arterial pressure, systemic vascular resistance, and rate-pressure product decreased (−15 (6)%, $p < 0·0001$; −23 (9)%, $p < 0·001$; and −12 (13)%, $p < 0·01$, respectively). The cardiac index and stroke volume index increased (+14 (9)%, $p < 0·05$; and 17 (15)%, $p < 0·01$, respectively). However, compared with placebo, the mean arterial pressure decreased more ($p < 0·01$) with enalapril, and after three hours the stroke volume index was increased ($p < 0·05$) and the rate-pressure product had fallen ($p < 0·01$). In contrast with the findings in the placebo group, pulmonary capillary wedge pressure decreased (−24 (25)%, $p < 0·01$) and after three hours the heart rate (−6 (7)%, $p < 0·05$) was slower. The changes seen during the absorptive phase were maintained into the postabsorptive phase (that is five hours after the start of the study). Except for a further decrease in heart rate, no changes were found between two, three, and five hours.

Overall changes from baseline values during the 12 hour study period were computed as areas under the curve (fig 2). Compared with placebo, enalapril reduced heart rate ($p < 0·05$), pulmonary capillary wedge pressure ($p < 0·05$), mean arterial pressure ($p < 0·01$), and rate-pressure product ($p < 0·01$).

Figure 1 Mean (SD) and individual changes (mean at baseline and at two hours (one hour after the first meal)) in the placebo group. See table 2 for abbreviations.



Enalapril group			
Baseline	*Absorptive phase*		*Postabsorptive phase*
0 h	*2 h*	*3 h*	*5 h*
87 (20)	85 (18)	81 (19)*	80 (15)**
5 (3)	4 (2)	5 (2)	4 (2)††
25 (7)	22 (5)	22 (5)	22 (5)†
15 (7)	11 (4)**	12 (4)*	12 (6)*††
83 (7)	71 (8)***††	69 (8)***†	70 (6)***††
2 3 (0 4)	2 6 (0 3)*	2 5 (0 3)	2 4 (0 7)
28 (9)	32 (9)**	33 (9)**†	31 (10)*†
1416 (288)	1067 (192)***	1035 (212)***	1150 (223)**
174 (63)	187 (44)	187 (48)	168 (39)
9833 (2077)	8522 (1779)**	7774 (1440)***††	7687 (978)***††

Discussion

This is the first placebo controlled, randomised double blind study showing the short term haemodynamic effects of an angiotensin-converting enzyme inhibitor in heart failure and the extent to which these effects are affected by eating, absorption, and postabsorption. In a group of patients with treated moderate heart failure caused by dilated cardiomyopathy, enalapril reduced left ventricular preload and afterload during both the absorptive and postabsorptive phases and hence throughout the 12 hour study period. Heart rate and the left ventricular metabolic cost, estimated as the rate-pressure product, decreased.

The principal features of central haemodynamic function during the absorptive phase (one hour after ingestion) were similar in controls and patients with varying degrees of heart failure.[12-16] Systemic vascular resistance decreased with or without decreases in mean arterial blood pressure and heart rate while the cardiac index increased. These systemic effects reflect absorptive splanchnic hyperaemia and are the result of a locally mediated vascular response to digested nutrients in the lumen[17] and their composition.[18 19] The hyperaemia seems to be limited to tissues that are active in digestion and was maximal after 30–90 minutes when the local blood flow increased 30–150%.[3 20 21] In healthy individuals splanchnic hyperaemia was paralleled by an increase in renal blood flow, but this haemodynamic response to food seemed to be specific to protein-rich meals.[22] Information on blood flow distribution to other vascular beds during the absorptive phase is scarce. Studies in animals suggest that blood flow to the brain and heart

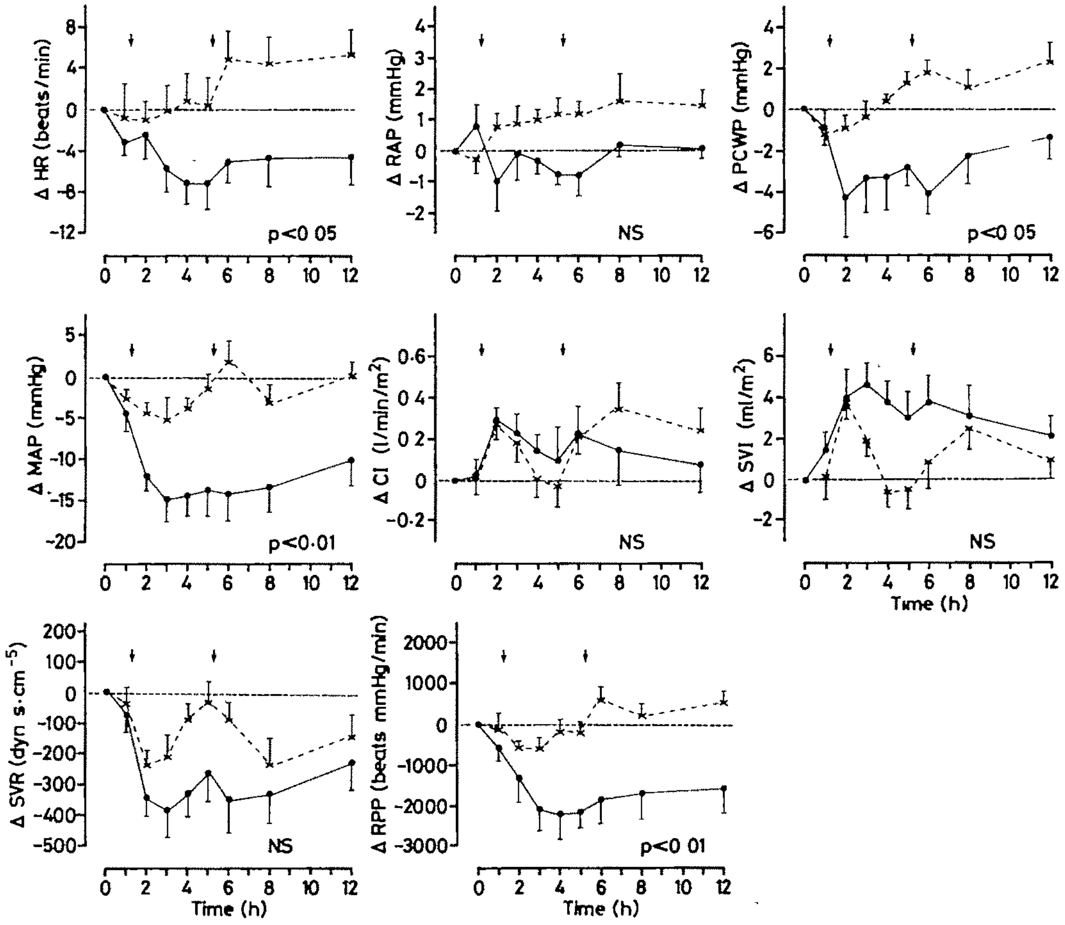


Figure 2 Absolute changes in haemodynamic measurements compared with baseline (mean (SEM)) after enalapril (●) and placebo (×). Arrows indicate meals. p values indicate differences between the two groups in the respective areas under the curve calculated from zero. See table 2 for abbreviations.

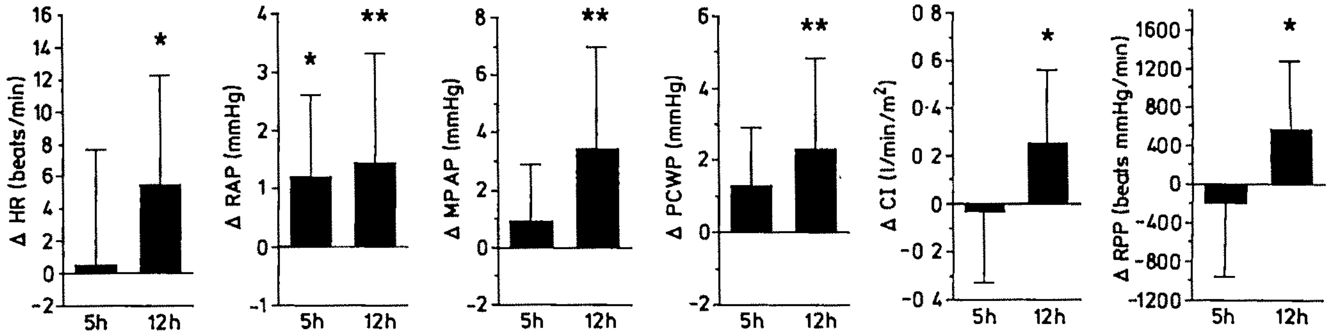


Figure 3 Spontaneous haemodynamic changes compared with baseline (mean (SD)) in the placebo group during postabsorptive phases at five and 12 hours. Significant differences from baseline as tested by analysis of variance are indicated as $^{*}p < 0{\cdot}05$ *and* $^{**}p < 0{\cdot}01$*. See table 2 for abbreviations.*

is unaltered and that to skeletal muscle is unaltered or reduced.[21] Although the central haemodynamic changes during the absorptive phase are similar in individuals with or without varying degrees of heart failure, the distribution of blood flow to other organs may differ with the cardiac capacity.

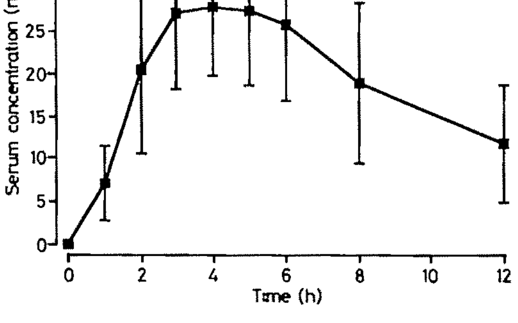
Packer *et al*[15] and Siemienczuk *et al*[16] reported a decrease in pulmonary capillary wedge pressure during the absorptive phase in patients with heart failure, but we found no change. This difference might be because our patients had a lower filling pressure. Differences in the selection of patients, study design, and spontaneous haemodynamic changes may be relevant.

We did not standardise the amount and composition of the meals eaten by our patients, who ate as much as they wanted and probably the same as they normally did.

In the placebo group we saw increases in heart rate, pressures, and cardiac index after 12 hours and in the postabsorptive phase. These results are at variance with those reported by Packer *et al*, who found a gradual decrease in pulmonary capillary wedge pressure during 24 hours after right heart catheterisation.[15] Massie *et al* reported similar results.[23] In contrast, we found increases in right atrial and pulmonary capillary wedge pressures after 12 hours and in the postabsorptive state, but we did not stop diuretics on the day of investigation. Diuresis during the morning could have added to lower filling pressures at baseline. Such differences in basal haemodynamic conditions underscore the importance of well defined basal conditions in order to avoid bias introduced by the design of a clinical trial.

Two hours after the oral administration of 10 mg of enalapril the serum concentration of enalaprilat was 20·4 (9·8) ng/ml. After 12 hours it was 11·7 (7·0) ng/ml. The serum concentration curve resembled that found in controls[6] and the time to peak concentration was not delayed, as has been reported in severe heart failure.[24] Angiotensin-converting enzyme inhibition in the 90% range was reported at only 10 ng/ml.[25] Therefore, angiotensin-converting enzyme inhibition was likely to be effective from the second to the twelfth hour of this study.

Figure 4 Concentration curve of serum enalaprilat (mean (SD)).



During the absorptive phase the reduction of afterload was more pronounced with enalapril than with placebo. Though the reduction of afterload during the absorptive phase in the placebo group was transient, it was maintained into the postabsorptive phase after enalapril. In addition, enalapril reduced heart rate and preload as expressed by a decreased pulmonary capillary wedge pressure while no change was seen in the placebo group. These enalapril induced changes increased from recordings during the absorptive phase to those of the postabsorptive phase, in keeping with short term pharmacodynamic studies on heart failure in which maximal haemodynamic effects, including heart rate and afterload reduction, were seen 4–8 hours after administration of a single oral dose.[6] So we would not expect the maximal afterload reduction in the enalapril group to occur as early as two and three hours after administration. Indices measured after two and three hours, however, resembled those measured five hours after administration. This indicates that after two and three hours, during the absorptive phase, the total reduction of afterload is a summation of enalapril-induced and meal-induced vasodilatation.

The patients were given diuretics on the day of investigation and this may have potentiated the haemodynamic changes produced by enalapril owing to complex interactions between diuretics and converting enzyme inhibitors.[26] Notwithstanding this fact, the aim of the study was to describe the short term haemodynamic effects of enalapril in an experimental situation that resembled, as far as possible, the daily routine of the patient at rest. In addition to meals, this routine also includes a continuation of long term medication.

In short term studies of congestive heart failure, inhibition of angiotensin-converting enzyme activity reduced systemic arterial pressure and systemic peripheral resistance and increased the cardiac index. In most vascular beds (limbs,[27–29] brain,[30] liver,[29] and coronaries[27 31]) tissue flow is maintained through homoeostatic vasodilatation. Information on splanchnic blood flow was ambiguous. The increase in the cardiac index was directed mainly to the kidneys where the regional blood flow was increased.[27 29] During the absorptive phase splanchnic vasodilatation induced by enalapril was supplemented by physiological splanchnic vasodilatation, which was probably caused by regionally active vasodilating agents.

CONCLUSIONS

(*a*) The principal haemodynamic effects of eating and absorption seemed to be similar in controls and patients with varying degrees of heart failure. After a meal there was a transient reduction of afterload and an increase in cardiac index. (*b*) When meals were being eaten regularly angiotensin-converting enzyme inhibition by enalapril in patients with moderate heart failure caused by dilated cardiomyopathy produced signs of a balanced reduction in preload and afterload with a decreased rate-pressure product. The afterload reduction was additional to that induced by meals. (*c*) To avoid bias in clinical trials the study design should be double blind with well controlled basal conditions.

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Left ventricular function during balloon dilatation of the aortic valve in elderly patients: a blind study of echocardiograms

Henrik Egeblad, Alf Wennevold

Abstract

Subcostal echocardiography of the left ventricle was continuously recorded during balloon dilatation of the aortic valve in ten consecutive elderly patients. Left ventricular wall motion decreased gradually during a minute of maintained complete balloon inflation. Blind analysis of M mode echocardiograms showed a significant reduction in fractional shortening. Deflation of the balloon resulted in global left ventricular hyperkinesia. There was a transient overshoot in fractional shortening, wall thickness, and blood pressure approximately 40 s after deflation of the balloon. The myocardial reaction was similar to that known to occur regionally with brief coronary artery obstruction, whereas the timing of the events seemed to be dissociated from the timing of changes in left ventricular load. Thus it is likely that the left ventricular response during valve dilatation reflects not only changes in load but also an ischaemia-reperfusion effect on the myocardium. The systolic thickening of the hypertrophied interventricular septum was slightly reduced after balloon dilatation. This finding might be a result of repeated episodes of ischaemia and reperfusion. However, the potential for myocardial injury seemed to be unimportant clinically.

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Balloon dilatation is increasingly used to treat elderly patients with aortic valve stenosis.[1–3] The cardiovascular response to the repeated inflations and deflations of the balloon is complex. Transient circulatory obstructions cause considerable changes in left ventricular load. In addition, ischaemia and reperfusion may have a direct and potentially injurious effect on the myocardium. Brief obstruction of a coronary artery is known to result in characteristic abnormalities in regional wall motion.[4–6] The aim of this study was to examine whether there are similar global myocardial reactions in the left ventricle during balloon dilatation of the aortic valve.

Patients and methods

We studied 10 consecutive patients (four men, six women; median age 76 years (range 72–87 years)) who underwent balloon dilatation of the aortic valve. All had clinical, electrocardiographic, radiological, and echocardiographic findings indicating severe stenosis of the aortic valve. Three of the patients had coexistent aortic valve incompetence that was considered to be haemodynamically insignificant on the basis of physical examination. None of the patients had primary mitral valve disease. Open heart operation for aortic valve stenosis was considered inappropriate because of the patient's advanced age or coexistent disease.

INVASIVE PROCEDURE

A 7 F pigtail catheter was introduced percutaneously into the femoral artery and advanced to the ascending aorta and on to the left ventricle with the aid of a guide wire. The peak gradient over the aortic valve was calculated as the difference between peak left ventricular systolic pressure and peak systolic pressure in the ascending aorta. The guide wire was used to replace the pigtail catheter by a Meditech 15 mm (3–4 cm) balloon catheter. The aortic valve was dilated with the centre of the balloon at the level of the aortic valve, which was apparent from the calcifications seen by fluoroscopy. The balloon was inflated with a mixture of saline and Urografin 76%. Inflation was maintained at constant maximum manual pressure for 60 s[1] unless the patient showed signs of insufficient cerebral perfusion. On fewer than 10 occasions was it necessary to deflate the balloon after 40 or 50 s because of vertigo, obvious dyspnoea, or when the patients speech became slowed. None of the patients lost consciousness or developed chest pain during the procedure.

Repeated dilatations were performed every 1–2 min, or more if the balloon catheter was replaced by a balloon of a larger size. Where possible dilatations were routinely carried out with balloons of increasing sizes from 15 to 18 or 20 mm in diameter. The procedure was stopped after 3–5 dilatations with the largest balloon. A median of eight (range 3–11) inflations of a balloon in the aortic ostium were carried out in the 10 patients.

Blood pressure was continuously recorded through an arterial sheath. Cardiac output was not measured. Because these were elderly patients we did not perform ventriculography, aortography, or coronary arteriography.

NON-INVASIVE PROCEDURE

Cross sectional and M mode echocardiograms from the parasternal, apical, and subcostal positions were recorded on video tape before and after balloon dilatation. During dilatation

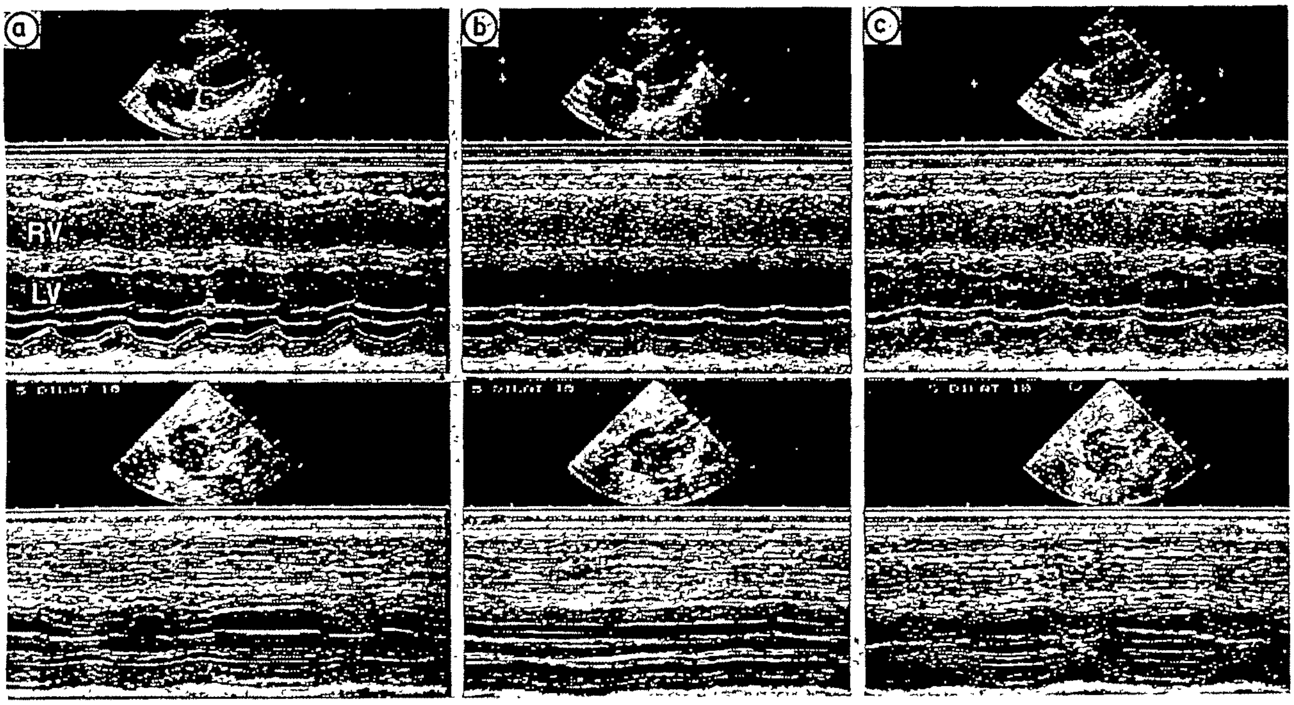

Figure 1 M mode echocardiograms guided by cross sectional subcostal four chamber view in two patients undergoing balloon dilatation of the aortic valve. Echocardiograms obtained immediately before balloon obstruction of the aortic valve (a); at the end of 1 min obstruction (b); and 40 s after deflation of the balloon (c). In one patient (above) the septum between right (RV) and left ventricle (LV) and the lateral wall (below LV) are clearly defined. The echocardiograms of the second patient (below) show even more pronounced hypokinesia during balloon obstruction and hyperkinesia during reperfusion, but the definition of the septum is more vague because of right ventricular obliteration in the projection selected

simultaneous cross sectional and M mode echocardiography were performed from the subcostal position. An M mode diameter through the left ventricle at the level of the chordae of the mitral valve was selected on the cross sectional four chamber view. Echocardiograms were continuously recorded on video tape before each inflation of the balloon, during maintained complete balloon inflation, and during and after deflation of the balloon (25 mm/s or 50 mm/s). Polaroid photographs were taken from the video tapes including recordings obtained before and after dilatation and immediately before and at the end of each balloon inflation (fig 1). In addition, Polaroid recordings were obtained from the video tape after each deflation of the balloon when left ventricular wall motion was re-established and seemed from the cross sectional image to be at its maximum (fig 1). Exaggerated respiratory movements occasionally distorted the echocardiogram. In these patients photographs were taken of the video tapes as close to the scheduled time as possible.

The identity of the patient and the timing of the recording were marked on the reverse of each photo. They were later shuffled and analysed in random order without knowledge of at what stage of the procedure they were obtained. We measured left ventricular diameter at end diastole (Dd) and end systole (Ds) and septal (ST) and lateral wall (LW) thickness. Left ventricular fractional shortening ($FS = ((Dd-Ds)/Dd) \times 100\%$) and thickening of the septum and lateral wall from diastole to systole were calculated. All measurements were obtained as mean values of 3–5 cycles.

The heart rate and number of runs of three or more ventricular extrasystoles in relation to inflation of the balloon were calculated from the continuously recorded electrocardiogram.

We used the Wilcoxon test for statistical analysis and a p value below 5% was regarded as significant.

Results

In the subcostal four chamber view the left ventricle appeared gradually to develop diffuse hypokinesia or akinesia over the 60 s period of maintained balloon inflation, with subsequent gradual development of global hyperkinesia after deflation of the balloon. These changes accorded with the measurements taken from the M mode recordings (figs 1 and 2). The median values and ranges shown in fig 2 include all values obtained immediately before inflation of the balloon, 60 (15–60) s after complete inflation, and 40 (10–60) s after the deflations. The most pronounced echocardiographic changes were associated with fractional shortening. There was a significant reduction from 30 (12–72)% before obstruction to 26 (9–56)% during obstruction and a significant increase to 43 (15–79)% after deflation. A reduction in systolic thickening of the lateral wall from 6 (1–13) mm before obstruction to 4 (0–10) mm during obstruction was statistically significant; systolic thickening of the septum was reduced from 4 (0–18) mm to 3 (0–14) mm ($p > 0\cdot05$). After deflation systolic thickening of both the lateral wall and septum increased to 7 (0–15) mm and 7 (0–18) mm respectively ($p < 0\cdot05$ for both).

The diastolic thickness of the septum and lateral wall did not change significantly during obstruction (before obstruction 16 (8–30) mm

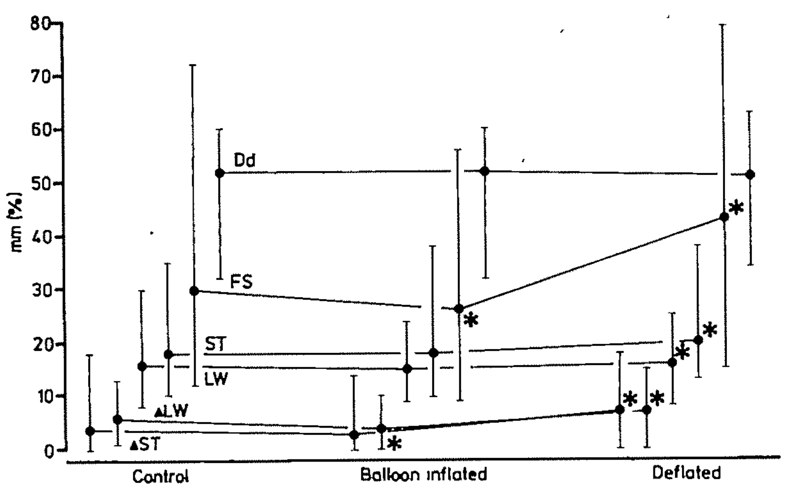

*Figure 2 Variation in left ventricular variables measured by subcostal echocardiography during balloon dilatation of the aortic valve. Median values and range are shown in 10 patients who had 8 (3–11) balloon inflations performed. Values measured after 60 (15–60) s obstruction of the aortic ostium are compared with pre-obstructive values obtained immediately before balloon inflation and with values measured 40 (10–60) s after deflation of the balloon. See footnotes to tables for abbreviations. *$p < 0\ 05$ compared with preceding value (rank sum test for paired data).*

for lateral wall thickness and 18 (10–35) mm for septal thickness compared with 15 (9–24) mm for lateral wall and 18 (10–38) mm for septal thickness during obstruction). Lateral wall thickness increased to 16 (8–25) mm and septal wall thickness to 20 (13–38) mm after deflation of the balloon ($p < 0\cdot05$ for both). Left ventricular diameter at end diastole did not change significantly, either from before obstruction (52 (32–60) mm) to the value measured after 60 s of obstruction (52 (32–60) mm) or that measured 40 s after deflation of the balloon (51 (34–64) mm).

Heart rate increased from 92 (64–135) beats/min before to 100 (65–122) beats/min during obstruction and slowed to 95 (64–135) beats/min 40 (10–60) s after deflation, but these variations were not statistically significant. Blood pressure fell from 105 (68–175)/50 (30–70) mm Hg to 68 (24–95)/38 (17–55) mm Hg from baseline to balloon obstruction ($p < 0\cdot05$ for systolic and diastolic blood pressure) and increased to 135 (65–195)/50 (30–100) mm Hg 40 (30–90) s after deflation of the balloon ($p < 0\cdot05$ for both). Only one episode of three or more runs of ventricular extrasystoles was recorded before balloon inflation whereas runs of ventricular extrasystoles were seen in 43% of the periods after inflation of the balloon (5 (0–12) s after inflation) and in 30% of the periods after deflation (45 (18–80) s after deflation).

Values recorded for the first cycle of balloon inflation and deflation and for the last cycle were not significantly different (table 1).

Data recorded before the procedure were compared with those obtained after the treatment (table 2). Aortic valve opening was significantly increased and the valve gradient and septal thickening decreased significantly.

Discussion

Previous studies showed that echocardiography may be a useful aid to guiding the balloon catheter and for evaluation of the result of balloon dilatation of the aortic valve.[7–9] Transoesophageal echocardiography in particular may facilitate stable and clear monitoring of the valve and left ventricle.[9] However, this technique requires general anaesthesia, which is best avoided in elderly patients and impedes the evaluation of the tolerance of decreased cerebral perfusion during balloon inflation. Parasternal M mode echocardiography of the left ventricle may be difficult to perform unless the patient is in the left lateral position, and interference between the ultrasound transducer, the hand of the examiner, and the fluoroscope, which is used to control the position of the balloon, is unavoidable.[10] Therefore, in this study we monitored left ventricular wall motion from the subcostal view. Continuous guidance by cross sectional echocardiography was helpful for maintenance of the direction of the M mode echocardiogram although optimum definition of the cardiac walls could not be obtained in all patients (fig 1). However, the reliability of the variations actually detected was endorsed by blind analysis of the echocardiograms and by previously reported experimental and clinical data.

Left ventricular hypokinesia during balloon obstruction—in this study recorded by echocardiography (figs 1 and 2)—has recently been confirmed by angiography.[11] Hypokinesia may occur because of the considerable increase in left ventricular afterload, but may also be a result of ischaemia. Reduction of cardiac output and aortic pressure owing to the balloon inflation together with possible obstruction of the coronary artery ostia may diminish myocardial oxygen supply. The ensuing reduction of the pump function might complete a vicious circle. The hypertrophy of the left ventricular myocardium (table 2) and possible coronary artery disease in some of the patients could further increase the sensitivity to reduced blood pressure, with the subendocardium being particularly jeopardised.[12] Coronary arteriography was not performed in our

Table 1 Data (median (range)) measured during balloon dilatation of the aortic valve

	Preobstructive control		*Balloon inflated*		*Balloon deflated*	
	First value	*Last value*	*First value*	*Last value*	*First value*	*Last value*
Dd (mm)	52 (40–59)	48 (39–60)	49 (35–56)	51 (34–59)	50 (40–59)	48 (34–57)
FS (%)	28 (19–58)	27 (12–79)	25 (13–43)	18 (14–56)	47 (17–57)	36 (20–65)
ST (mm)	17 (13–32)	17 (13–35)	18 (12–31)	18 (13–28)	18 (14–28)	18 (15–34)
LW (mm)	13 (11–18)	13 (11–22)	14 (9–18)	13 (10–24)	16 (10–20)	15 (8–22)
ΔST (mm)	4 (1–9)	3 (0–12)	4 (2–7)	3 (0–9)	5 (0–12)	5 (1–12)
ΔLW (mm)	6 (4–8)	6 (2–9)	4 (3–10)	3 (1–7)	6 (0–15)	6 (4–14)
Systolic BP (mm Hg)	125 (80–158)	145 (68–160)	75 (52–95)	50 (35–65)	140 (65–165)	135 (74–168)
Diastolic BP (mm Hg)	50 (40–62)	50 (30–64)	40 (35–55)	37 (25–50)	42 (38–65)	45 (42–60)
HR (beats/min)	84 (70–107)	98 (70–112)	90 (78–110)	90 (68–122)	90 (82–115)	99 (68–118)

Left ventricular characteristics by subcostal echocardiography, heart rate (HR), and blood pressure (BP) measured initially and late during the course of balloon dilatation of the aortic valve Dd, left ventricular diastolic diameter, FS, left ventricular fractional shortening; LW, lateral wall thickness in diastole; ΔLW, systolic thickening of the lateral wall, ST, thickness of the interventricular septum in diastole, ΔST, systolic thickening of the interventricular septum.

Table 2 Data (median (range)) measured before and after balloon dilatation of the aortic valve

	Before	*After*
Time of examination in relation to procedure (days)	3 (1–7)	4 (1–11)
	Parasternal echocardiography	
Aortic cusp separation	4 (3–6)	6 (3–9)*
Dd (mm)	52 (39–62)	58 (37–65)
Ds (mm)	38 (24–52)	43 (15–51)
FS (%)	32 (17–40)	29 (14–59)
ST (mm)	15 (12–18)	15 (12–20)
PW (mm)	12 (8–17)	13 (10–15)
	Subcostal echocardiography	
Dd (mm)	53 (37–63)	55 (37–59)
Ds (mm)	38 (18–52)	39 (18–48)
FS (%)	28 (14–51)	24 (16–53)
ST (mm)	17 (13–34)	17 (14–37)
LW (mm)	14 (10–21)	13 (12–21)
ΔST (mm)	5 (0–9)	3 (0–7)*
ΔLW (mm)	5 (2–8)	5 (2–12)
HR (beats × min^{-1})	85 (65–107)	90 (72–107)
BP (mm Hg)	130 (100–155)/ 70 (60–100)	130 (100–165)/ 80 (60–90)
Aortic valve gradient immediately before and after procedure (mm Hg)	80 (30–125)	30 (0–55)*

Left ventricular characteristics, heart rate (HR), and blood pressure (BP) before and after balloon dilatation of the aortic valve Dd, left ventricular diastolic diameter, Ds, left ventricular systolic diameter, FS, left ventricular fractional shortening, LW, lateral wall thickness in diastole; ΔLW, systolic thickening of lateral wall; PW, posterior wall thickness in diastole, ST, thickness of the interventricular septum in diastole; ΔST, systolic thickening of the interventricular septum *$p < 0.05$.

patients, none of whom developed angina pectoris during balloon dilatation. However, transient ST-T depression was often seen on the monitor electrocardiogram. The ST-T depressions were not measured because electrocardiographic mapping would have interfered with the fluoroscopy. Furthermore, bundle branch block and treatment with digoxin may interfere with the measurement and interpretation of ST-T changes in many elderly patients with aortic stenosis.

Complete coronary artery obstruction by ligation leads to regional dyskinesia within a minute.[4,13] Dyskinesia is often noticed in anterior wall infarction with Q waves but rarely in non-Q wave infarction and in pathoanatomical subendocardial infarction.[14,15] Most of our patients showed hypokinesia during balloon inflation but a few showed akinesia (fig 1). Dyskinesia did not occur. Left ventricular wall motion gradually became hypokinetic or akinetic within 60 s of complete inflation of the balloon. The left ventricular diameter at end diastole did not change significantly (fig 2). Thus the increase in left ventricular load remained constant while the balloon was kept inflated. Increased afterload doubtlessly contributed to the left ventricular response when the balloon was kept inflated. However, the timing and character of the wall motion abnormality were compatible with the concept of subendocardial ischaemia as a determinant of the development of hypokinesia and akinesia during the balloon obstruction. This hypothesis is supported by the recent demonstration by catheterisation of the coronary sinus of transient low flow ischaemia during balloon inflation.[16]

The response of the left ventricle to deflation of the balloon included transient hyperkinesia of the left ventricular walls that reached a maximum 40 s after the start of deflation. There was no significant change in the left ventricular diameter at end diastole. Deflation of the balloon led to a reduction of the left ventricular afterload. A decrease of peripheral vascular resistance is likely to occur at the same time. Cardiac output was not monitored in this study but a reduction in peripheral vascular resistance was recognised in studies of declamping after aortic surgery.[17] The reduction in afterload resulting from the balloon deflation and the potential reduction of peripheral vascular resistance accord with the suggestion that there is left ventricular hyperkinesia after obstruction by the balloon. However, reperfusion of the myocardium may contribute significantly to the increased wall motion. A hyperkinetic wall motion response, which was attributed to sudden cellular calcium influx, was seen in experimental and clinical studies after the abolition of brief regional myocardial ischaemia.[4,5,13] In animal experiments ligation of the coronary artery for a minute resulted in maximum hyperkinesia after 40 s of reperfusion.[13] A similar time course of hypokinesia and hyperkinesia was seen in variant angina.[18] Furthermore, the significant increase in diastolic wall thickness after deflation of the balloon resembles the findings at coronary artery reperfusion in the experimental setting.[13,19] The increase in wall thickness has been attributed to engorgement of the myocardial vascular bed during reactive hyperaemia. The gradual increase in left ventricular wall motion and systolic blood pressure during reperfusion, with an overshoot in both after 40 s and a simultaneous diastolic blood pressure value at the pre-obstructive level are likely to reflect myocardial reperfusion rather than a decrease of afterload. The reduction in afterload may be greatest immediately after the balloon deflation. Finally, the occurrence of arrhythmias after deflation of the balloon indicates a reperfusion effect on the myocardium.[20]

The variation in fractional shortening was further analysed to obtain a clearer idea of the time course of the myocardial response to inflation and deflation of the balloon (fig 3). To limit the number of measurements, the analysis was confined to two patients. Their M mode video recordings of the left ventricle were stable and during all aortic valve dilatations the balloon was completely inflated for 60 s. The number of balloon inflations in both these patients resembled the median number of dilatations (eight) in the study population. The two patients are not those shown in fig 1. An additional 161 photographs were obtained from the two patients' video tapes immediately before the procedure and every 15 s during and after 60 s of maintained complete inflation of the balloon. Fractional shortening was measured without knowledge of the timing of the recordings. There was no significant reduction of fractional shortening until late during the 60 s period of maintained inflation (fig 3). Other data from our laboratory showed that the time needed for complete filling and emptying of the balloon was approximately 20 s. Figure 3 indicates that there was no reduction of fractional shortening during filling of the balloon

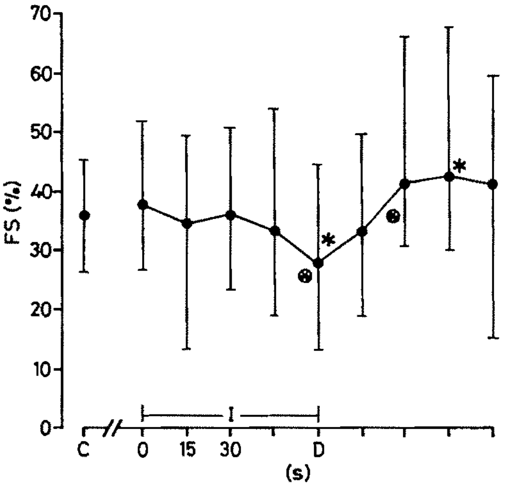

Figure 3 Fractional shortening (median and range) recorded every 15 s in two patients (1 M, 1 F) in whom seven and 10 balloon inflations and deflations were performed C, value recorded immediately before the procedure. I, the 60 s period during which complete balloon inflation was maintained. Deflation started at D. In most cases a new balloon inflation was carried out 60 s after D. Open asterisks, $p < 0{\cdot}05$ compared with control value; closed asterisks, $p < 0{\cdot}05$ compared with value 15 s before (rank sum test for paired data).

(before I in fig 3). Therefore, partial obstruction of the aorta during emptying of the balloon cannot be regarded as a likely explanation of the delay of maximum wall motion hyperkinesia (fig 3). Furthermore, the entire delay of 40–45 s after the start of deflation cannot be explained by the 20 s needed to deflate the balloon completely. However, the time course of fractional shortening during inflation and deflation of the balloon is similar to the time course of regional wall motion observed in experimental ischaemia and reperfusion.[13]

Recent studies have shown minor improvement of ejection fraction immediately, early, and late after balloon dilatation of the aortic valve.[2,21] Fractional shortening did not change significantly after balloon dilatation in this study (table 2). This does not exclude an increase in overall systolic function because only the function of myocardial fibres at the base of the ventricle is reflected in fractional shortening.

Throughout the procedure there were insignificant reductions in fractional shortening and systolic septal thickening (table 1). However, the pre-obstructive values of fractional shortening and systolic septal and lateral wall thickening before the last balloon inflation may have been artificially increased by the post-obstructive wall motion hyperkinesia induced by the balloon deflation that immediately preceded inflation (fig 3). In animal experiments it took at least two minutes for hyperkinesia to disappear after a minute of coronary artery ligation.[13] Our study showed a slight decrease of the systolic thickening of the septum after the procedure (table 2). The proximal part of the septum is commonly the site of the most prominent hypertrophy in aortic stenosis. Reduction of systolic septal thickening soon after dilatation may show that hypertrophied myocardium is particularly susceptible to ischaemia and reperfusion and thus may be a manifestation of stunned myocardium.[22] However, the technique used for balloon dilatation of the aortic valve and the improvement of valve gradient and the clinical condition of the patients were similar to those reported in previous studies.[1] Thus the minor reduction of systolic septal thickening can be regarded as clinically insignificant.

In our blind echocardiographic study of the left ventricular response to balloon dilatation of the aortic valve we found significant changes in left ventricular wall motion and wall thickness in relation to inflation and deflation of the balloon. The changes in left ventricular load undoubtedly contributed to the myocardial reactions but their character and time course resembled those seen in experimental and clinical ischaemia and reperfusion. Thus myocardial ischaemia and reperfusion may be important determinants of the left ventricular response to balloon dilatation of the aortic valve, and the potential impact on the myocardium of repeated ischaemia and reperfusion should be considered when percutaneous balloon dilatation of the aortic valve is performed.

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Open valvotomy for critical aortic stenosis in infancy

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Abstract

Over a 5 year period open valvotomy was performed on 13 patients under the age of one year with critical aortic stenosis. All 13 survived operation. There were two late deaths—one 38 days after operation, associated with an unrelated neurosurgical procedure and the other 2 years 6 months after when aortic root enlargement and replacement of the aortic valve were performed. During this period two other infants presented with aortic stenosis. One, who was very ill before transfer, died before operation could be performed. The second patient had a hypoplastic left ventricle with a small mitral valve ring and was, therefore, considered to be part of a different subgroup. All the surviving children have been followed up (median length of follow up 2 years and 11 months, range 7 months–5 years). Left ventricular function, in terms of percentage systolic wall thickening, was shown to be significantly impaired in all age groups. Peak diastolic thinning was abnormal in those children aged from 3 to 5. The aortic valve gradient, as assessed by peak instantaneous continuous wave Doppler, was < 40 mm Hg in five patients and between 40 and 70 mm Hg in seven patients. One patient, with appreciable restenosis, has undergone successful percutaneous balloon dilatation of the aortic valve.

The mortality for aortic valvotomy in children over one year of age is low.[1,2] In contrast, mortality is high in those below the age of one year. Various operative techniques have been used in infancy including circulatory arrest and hypothermia,[3] inflow occlusion and partial cardiopulmonary bypass,[4] inflow occlusion alone,[5–7] cardiopulmonary bypass[2,8,9] transventricular valvotomy with blunt dilatation,[10,11] and transventricular balloon dilatation of the valve.[12,13] The surgical mortality in these studies has varied from 9% to 66%. Recently, small series treated by percutaneous balloon dilatation have been reported.[14–16] In the largest series published so far mortality was high[17–19] and transverse tears of the aortic wall were reported with this technique.[20] Our preferred technique is open surgical valvotomy with conventional cardiopulmonary bypass. We report our results over a 5 year period.

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Patients and methods

From September 1982 to September 1987, 13 patients presented with critical aortic stenosis. Their median age was 14 days (range 1–91) and the median weight was 4·0 kg (range 2·2–6·4). Endocardial fibroelastosis was present in four patients. Three patients were pulseless and poorly perfused at presentation—one of them had an initial pH of 6·9 and the other two were resuscitated with immediate ventilation and intravenous bicarbonate before blood gases were measured. Seven patients presented with heart failure. Three were symptom free and the gradients from left ventricle to ascending aorta were therefore investigated. Two of these patients underwent preoperative cardiac catheterisation (no other patients were catheterised before operation); the third had ST segment depression on an electrocardiogram and the aortic valve gradient was assessed by continuous wave Doppler. The mean gradient of these three (left ventricle to aorta) was 120 mm Hg. None of the 13 patients had a hypoplastic left ventricle by echocardiographic criteria.[2,21] Another two patients were excluded. One patient had disseminated intravascular coagulation, necrotising enterocolitis, and a pulmonary haemorrhage before transfer to our institution and died before operation could be performed. The other had a hypoplastic left ventricle. At echocardiography the diameter of the mitral valve was < 10 mm and the ventricle was spherical with a maximum transverse cavity dimension of 6 mm. This is in keeping with previously described criteria for diagnosing a hypoplastic left ventricle. Although this patient underwent valvotomy he died after operation. He was considered to be part of a separate subgroup and to have died as a consequence of a small mitral valve annulus and a small left ventricle.

METHODS

All patients had an open aortic valvotomy. Conventional cardiopulmonary bypass with moderate hypothermia was used in 11 patients and inflow occlusion in two patients.

Eleven of the patients were studied with continuous wave Doppler (Doptech scanner), cross sectional echocardiography, and M mode echocardiography and the other patient was studied by Doppler flow at another hospital. Investigations were performed at a median of 2 years 11 months (range 7 months–5 years) after operation. Of the 11 M mode echocardiograms, 10 were of sufficiently high quality to enable digitisation to be performed (fig 1) as previously described.[22] Three beats were digitised from each patient. Left ventricular cavity dimensions and posterior wall thickness were measured throughout the cardiac cycle (fig 2). From these we obtained indices of systolic function (percentage systolic wall thickening, fractional left ventricular shortening (%), peak rate of systolic wall thickening (cm/s) and diastolic function (peak rate of diastolic wall thinning cm/s, and peak rate of left ventricular filling cm/s) (fig 3).

All data were expressed as mean (1 SD). Variables were compared by Student's t test. The null hypothesis was rejected if $p < 0\cdot05$.

We compared results obtained with previously reported normal ranges for children aged 1–3 and 3–5 years from our hospital.[23]

Results

There was no operative mortality. One patient died 38 days after operation during an unrelated neurosurgical procedure. The mean peak instantaneous gradient at recent continuous wave Doppler was 41 mm Hg (range 8–70 mm Hg). A gradient of between 40 and 70 mm Hg was found in seven patients (fig 4) and one has recently undergone successful percutaneous balloon dilatation of the aortic valve. There was no relation between age and Doppler gradient. Two patients had significant aortic incompetence clinically and echocardiographically; recently one of them underwent aortic root enlargement and aortic valve replacement (19 mm St Jude prosthesis) 2 years and 6 months after her initial operation. At operation the valve was found to be bicuspid and the original incision that had been taken to one side of the anterior commissure was believed to be causing the incompetence. The postoperative course was complicated by poor ventricular function and recurrent ventricular tachycardia and the patient died on the 23rd postoperative day.

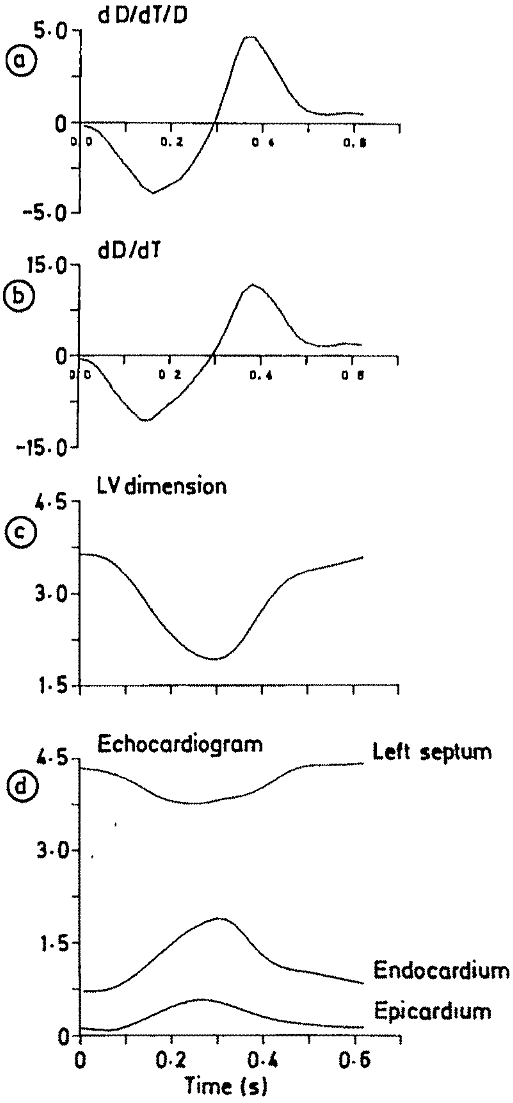

Figure 2 Computer output of digitised echocardiogram: (a) normalised rate of change of dimension (d D/dt/D) (per s); (b) rate of change of left ventricular dimension (d D/dt) (cm/s); (c) instantaneous change in left ventricular (LV) dimension (D) (cm); (d) digitised M mode echocardiogram (cm).

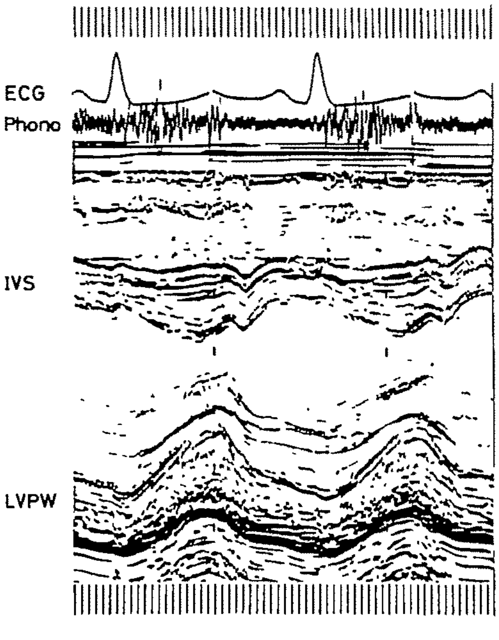

Figure 1 M mode echocardiogram of the left ventricle at the level of the mitral valve from a 3 year old patient with previous critical aortic stenosis. ECG, electrocardiogram; phono, phonocardiogram; IVS, intraventricular septum; LVPW, left ventricular posterior wall.

The table shows indices of systolic and diastolic function obtained from the M mode echocardiograms. The mean heart rates were 117 (19) (1–3 years) and 99 (24) (3 to 5 years) per minute, which resemble normal rates.[21] There was significant reduction in the value of percentage systolic wall thickening ($p < 0\cdot001$) in children in both age groups (1·5–3 years and 3–5 years). Peak diastolic thinning was decreased in the group aged 3–5 years ($p < 0\cdot02$). Other values were not significantly abnormal. There was only one patient under 1·5 years of age and, although digitisation was performed, there are no normal data with which to compare the results in this patient. However, if the values are compared with the 1·5–3 year group then peak left ventricular filling and percentage systolic wall thickening were significantly decreased ($p < 0\cdot001$) as were peak diastolic thinning and fractional left ventricular shortening ($p < 0\cdot01$). In the child who died after aortic root enlargement and aortic valve replacement percentage wall thickening (34·6%) was decreased and fractional left ventricular shortening (20·5%) was considerably reduced.

Discussion

Our study showed that during the 5 year period

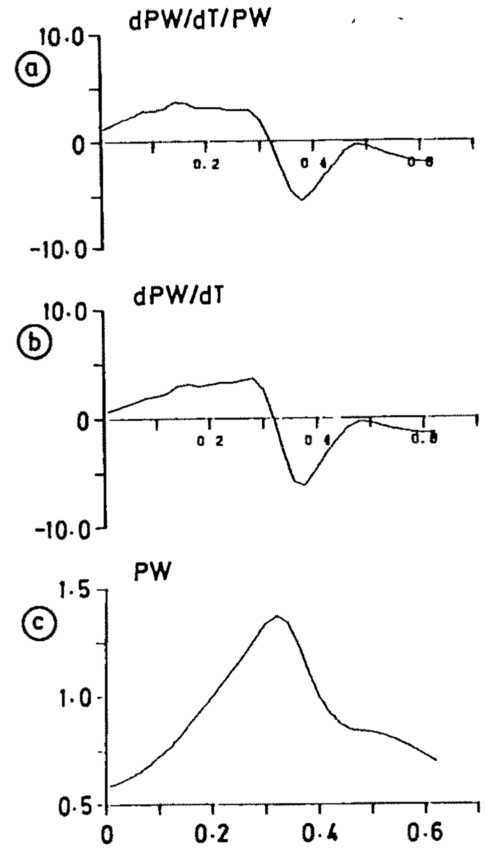

Figure 3 Computer output of digitised echocardiogram: (a) normalised rate of change of left ventricular posterior wall thickness, (b) instantaneous rate of change of left ventricular posterior wall thickness; (c) posterior wall (PW) thickness measured continuously.

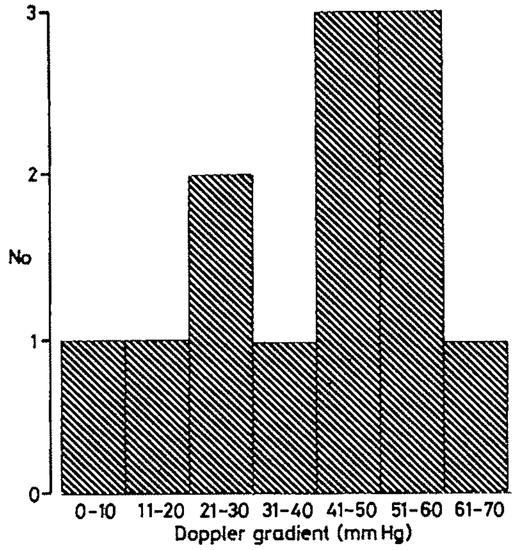

Figure 4 Distribution of peak instantaneous gradients from the left ventricle to the aorta as measured by continuous wave Doppler.

from September 1982 to September 1987 open aortic valvotomy for critical aortic stenosis in infancy was not associated with any early (30 day) mortality. However, we excluded a patient who retrospectively we considered to have a hypoplastic left ventricle by established echocardiographic criteria[2 21] and who died in the postoperative period. We view patients with hypoplastic left ventricle as a subgroup in which others have shown a 100% mortality for aortic valvotomy.[24 25] Our current practice is to consider these patients for a Norwood procedure.[26] If, where possible, the deaths of patients with hypoplastic left ventricle are excluded from the series of patients undergoing balloon dilatation of the aortic valve, then the early mortality is 54% and 100% respectively[17 19]; however, in another study early mortality was only 19% for all patients.[18]

Our retrospective study highlights the need for careful follow up. Although all the survivors are well, seven patients had a gradient of between 40 mm Hg and 70 mm Hg on continuous wave Doppler. Two patients had considerable aortic incompetence. One patient died after enlargement of the aortic root and replacement of the aortic valve. To date, none of our other patients has required reoperation, but one has undergone percutaneous balloon dilatation of the aortic valve. It is likely that others will need further relief of aortic stenosis in the near future.

Left ventricular function (in terms of percentage systolic wall thickening) was abnormal in children aged 1·5–3 years and those aged 3–5 years. In addition, diastolic function (in terms of peak diastolic thinning) was significantly decreased in the group aged 3–5 years. This may reflect the increase in fibrous tissue in the left ventricle that has been described in adults with aortic stenosis.[27] Other indices were reassuringly normal. Longer term follow up will be required to assess the clinical implications of these abnormalities of systolic and diastolic function.

Recently a mortality of 15% for open aortic valvotomy in infants over a 13 year period with no deaths since 1979 has been reported.[28] However, the patients were slightly older at presentation than the ones we described (median age 8 weeks as opposed to 2 weeks). Allied with the low mortality for open valvotomy at our hospital, this produces a firm background of contemporary data against which other procedures should be judged. At present we hesitate to adopt a policy of primary percutaneous balloon dilatation of the aortic valve in infancy. The mean Doppler gradient across the aortic valve at follow up in the recent series[28] was similar to the one that we report (mean 43 mm Hg compared with 41 mm Hg) but we found fewer patients with aortic regurgitation. It seems likely, therefore, that intervention will be necessary in several patients in the future. At repeat valvotomy the valve cusps have been described as flexible and non-calcified in most, suggesting maturation of

Left ventricular (LV) systolic and diastolic function at follow up (mean (1 SD))

Age (yr)	*Peak rate of diastolic thinning (cm/s)*	*Peak rate of LV filling (cm/s)*	*Systolic wall thickening (%)*	*Fractional LV shortening (%)*	*Peak rate of systolic wall thickening (cm/s)*
<1·5 (n = 1)	3·0 (0·1)	5·3 (0·1)	23·4 (3·1)	21·7 (3·1)	2·5 (0·7)
1·5–3 (n = 5)	3·9 (1·24)	9·64 (1·83)	38·40 (10·30)	31·9 (6·7)	2·76 (0·81)
Normal range	(5·0 (1·4))	(9·2 (1·3))	(113 (24))	(32 (7))	(2·9 (1·0))
3–5 (n = 5)	4·37 (2·12)	10·17 (4·15)	36·37 (14·18)	39·5 (8·2)	2·92 (0·88)
Normal range	(8·6 (2·0))	(11·2 (3·7))	(107 (39))	(34 (3))	(3·2 (1·2))

the original embryonal structure.[6] We have, therefore, performed percutaneous balloon dilatation of the aortic valve when repeat valvotomy has been required.

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Doppler echocardiographic characteristics of normal and dysfunctioning prosthetic valves in the tricuspid and mitral position

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Abstract

The Doppler echocardiographic characteristics of 70 prosthetic valves in 35 patients are reported. Twenty nine patients had a Bjork-Shiley prosthesis in both mitral and tricuspid positions and six had Carpentier-Edwards valves in both sites. Five of the patients had abnormal tricuspid prostheses on the basis of clinical and echocardiographic criteria. Pulsed wave Doppler echocardiography was used in all examinations. The pressure half times for the normal tricuspid prosthetic valves, 105 (40) ms (Björk-Shiley) and 97 (53) ms (Carpentier-Edwards), were significantly longer than those of normal mitral prosthetic valves, 75 (18) ms (Björk-Shiley) and 83 (15) ms (Carpentier-Edwards). The range of pressure half times for the abnormal tricuspid valves (237–530 ms) was distinct from that of the apparently normal tricuspid prosthetic valves (38–197 ms). There was an increase in the peak velocity of the obstructed tricuspid prosthetic valves (1·69 (0·12) m/s) in comparison with normal prostheses (1·06 (0·26) m/s).

The normal range of pressure half times for the Björk-Shiley and Carpentier-Edwards valves in the mitral position is not applicable to the same valves in the tricuspid position. The valve appears to function well with very long pressure half times but a pressure half time of >200 ms coupled with a peak velocity of greater than 1·60 ms without significant valve regurgitation indicates tricuspid obstruction of the tricuspid prosthetic valve.

The detection of prosthetic valve dysfunction often poses a diagnostic challenge because symptoms and signs of dysfunction are often non-specific and can be difficult to detect and measure on clinical examination. The reference standard of investigation for valve function has been cardiac catheterisation (with careful measurement of pressure gradients) and angiography. However, there are practical problems and risks in using invasive methods of assessment, because either the prosthetic valve has to be crossed or direct ventricular puncture attempted in the case of tricuspid prosthetic valves.

It is now widely accepted that Doppler echocardiography provides more detailed and accurate information on the severity of prosthetic valve dysfunction than any other non-invasive procedure.[1,2] Although there are many recent studies on the value of Doppler echocardiography in the assessment of mitral and aortic prosthetic valves,[1-5] there is very little information on the Doppler examination of normal or abnormal tricuspid prosthetic valves[6,7] and the numbers reported are small. This study was performed to define a normal range of Doppler indices for the Björk-Shiley tilting disc valve and Carpentier-Edwards xenograft in the tricuspid position and compare them with the same prostheses in the mitral position. We also describe the Doppler characteristics of five clinically dysfunctioning tricuspid prosthetic valves.

Patients and methods

Thirty five patients were studied; all had undergone mitral and tricuspid valve replacement with the same valve type in both sites. Twenty nine patients had Björk-Shiley (tilting disc) and six had Carpentier-Edwards (xenograft) valve prostheses. Symptoms and clinical and radiographic examinations showed normal mitral prostheses in all patients. In five patients an abnormal tricuspid prostheses was suspected on the basis of the following findings:

(*a*) Symptoms suggestive of declining cardiac output—for example increasing muscle fatigue on exercise and decline in exercise tolerance with evidence of a significantly raised jugular venous pressure, hepatomegaly, and peripheral oedema.

(*b*) The absence of significant right or left ventricular dysfunction on echocardiographic examination.

Thirty two of the patients were in atrial fibrillation and three were in sinus rhythm. The time from implantation to study ranged from 6 months to 18 years (mean 9·5 years). Valve sizes for the tricuspid position ranged from 27 to 33 mm and for the mitral position from 25 to 31 mm. There were 21 standard and eight monostrut type Björk-Shiley valves. The patients' ages ranged from 21 to 75 years (mean 59 years). There were 26 women and nine men. Fifteen normal volunteers formed a control group with native valves.

Pulsed wave Doppler echocardiography with a 3·5 MHz imaging transducer was used in all the studies and all of the Doppler spectral recordings were obtained by one observer. The pulsed Doppler sample volume (3 mm^3 was located just distal to the tip of the valve leaflets or the tilting disc. The position of the

Table 1 Comparison of pressure half times for tricuspid and mitral prosthetic and native valves

Valve type	No	Pressure half time (ms) Mean (SD)	Median	Range
Tricuspid valves:				
Normal Björk-Shiley	24	105 (40)*	108	50–195
Normal Carpentier-Edwards	6	97 (53)*	107	38–197
Normal native valve	15	67 (15)***	69	41–71
Obstructed Björk-Shiley	5	353 (130)**	308	237–570
Mitral valves				
Normal Björk-Shiley	29	75 (18)*	71	71–120
Normal Carpentier-Edwards	6	83 (18)*	79	79–110
Normal native valve	15	(11)***	53	53–65

*$p \leqslant 0{\cdot}01$, difference between mitral and tricuspid normal prosthetic valves.
**$p \leqslant 0{\cdot}001$, difference between obstructed and normal tricuspid prosthetic valves.
***$p \leqslant 0{\cdot}01$, difference between mitral or tricuspid normal prosthetic and native valves.

transducer was adjusted to obtain the highest maximum velocity with the least velocity dispersion, according to the audio signal and spectral display. The transducer position (apical or parasternal) used to measure the mitral and tricuspid velocities depended on the flow characteristic of the valve. The best alignment with the Doppler beam for native valves and xenografts was often the same because both had central flow characteristics. As expected with the tilting disc valve in the mitral position the major jet was often directed eccentrically towards the interventricular septum. The tricuspid prostheses were orientated with the large orifice opening anteromedially because in patients with considerable right ventricular hypertrophy more conventional posterior opening of the prosthesis could lead to the disc impinging on the subannular posterior wall of the hypertrophied right ventricle. Somewhat modified transducer positions were necessary to obtain optimal and clear spectral recordings in the group with tricuspid prostheses.

To measure peak velocities the maximum peak detected during the examination was recorded over at least 10 cardiac cycles. Atrioventricular pressure half times were recorded over a minimum of seven cardiac cycles and the average of these readings was taken. Pressure half time was calculated by on line computer software as the time taken for the peak velocity to fall to peak velocity/1·4 according to the method of Hatle *et al.*[8] To assess the severity of valve regurgitation, systolic flow in the relevant atrium was studied in all patients by pulsed Doppler mapping of the chamber with small movements of the transducer and shifts of sample volume position from apical and modified parasternal positions. Valve regurgitation was graded according to the depth and width of the systolic jet detected: mild—jet no more than 2 cm from the valve ring with a jet width <5 mm; moderate—jet ⩽2 cm from the valve ring but >5 mm wide or jet detected >2 cm from the valve ring into the atrium but not reaching the posterior third of the atrium; severe—jet >5 mm wide detected in the posterior third of the atrium.

Intraobserver variability was studied by an analysis of the recordings. There was a mean difference of <5% for measurements of the same spectral display.

STATISTICAL ANALYSIS

Peak velocities and pressure half times across the mitral and tricuspid prosthetic and native valves were compared by the paired or unpaired *t* test as appropriate. We used a rank correlation test to compare the peak velocities or pressure half times and time since implantation.

Results

PRESSURE HALF TIME

Table 1 shows the results of pressure half times for normal and abnormal prosthetic mitral and tricuspid valves and native valves. There was no significant difference between the pressure half times for prosthetic valves of different sizes in either the mitral or tricuspid position. There was no significant difference between the pressure half times of the monostrut or standard Björk-Shiley prostheses.

There was also no correlation between pressure half time and time since implantation in either the mitral or tricuspid positions. The pressure half time was significantly greater in the tricuspid position than in the mitral position for both normal Björk-Shiley and Carpentier-Edwards valves. The pressure half time was significantly longer in the dysfunctioning Björk-Shiley tricuspid valves than in the apparently normal prosthetic valves. Beat to beat variation in pressure half times ranged from 0 to 35 ms (mean 16) for the mitral valve

Table 2 Comparison of peak early velocity for tricuspid and mitral prosthetic valves

Valve type	No	Peak velocity (m/s) Mean (SD)	Median	Range
Tricuspid valves.				
Normal Carpentier-Edwards and Björk-Shiley	30	1·06 (0·26)	1·145**	0·6–1·6
Normal native valve	15	0·54 (0·11)	0·590***	0·34–0·94
Obstructed Björk-Shiley	5	1·69 (0·12)	1·730*	1·53–1·94
Mitral valves.				
Normal Björk-Shiley and Carpentier-Edwards	35	1·17 (0·25)	1·200**	0·4–1·75
Normal native valve	15	0·86 (0·32)	0·960***	0·4–1·3

*$p \leqslant 0{\cdot}01$, difference between obstructed and normal tricuspid prosthetic valves.
**p = NS, difference between normal tricuspid and mitral prosthetic valves.
***$p \leqslant 0{\cdot}01$, difference between normal native, mitral and tricuspid valves.

Table 3 Frequency and degree of valve regurgitation

	Valve regurgitation (No)	(%)	Degree (mild-severe)
Normal Björk-Shiley:			
Mitral	3/29	10·0	Mild
Tricuspid	3/24	12·5	Mild
Normal Carpentier-Edwards:			
Mitral	1/6	16·0	Mild
Tricuspid	1/6	16·0	Mild
Dysfunctioning Björk-Shiley:			
Tricuspid	2/5	40·0	Mild

and from 10 to 95 ms (mean 46) for the tricuspid valve.

PEAK VELOCITY

Table 2 shows the results for all the peak velocities. There was no significant difference between the peak velocities of normally functioning prosthetic valves in either the mitral or tricuspid position. There was a significant difference between the peak velocity of native mitral and tricuspid valves. The peak velocity of the obstructed valves was significantly higher than in prosthetic tricuspid valves with apparently normal function. Once again there was no significant difference or trend between the peak velocities for different sized valves and no correlation between peak velocity and time since implantation in either position.

VALVE REGURGITATION

Table 3 shows the results of the regurgitation study. Valve regurgitation was more common in the normal Carpentier-Edwards valves than in the normal Björk-Shiley valves. There was a significantly higher incidence of regurgitation in the five patients with dysfunctional valves but in all cases this was mild.

Discussion

The normal value for pressure half time across the native mitral valve was reported to be < 60 ms,[8] but surprisingly there are no data on normal pressure half times for the native tricuspid valve. There is very little published information on the Doppler indices for normal or abnormal native or prosthetic tricuspid valves.[5–7 9 10] These studies of small numbers of normally functioning tricuspid xenografts reported pressure half times ranging from 67 to 260 ms. There are few data on tricuspid prostheses because there is no satisfactory method of recording right ventricular pressure and hence mean pressure gradients without transthoracic puncture of the right ventricle or crossing the prosthetic valve with a catheter.

Both mechanical and biprosthetic valves cause some obstruction of blood flow even when they function normally and this is reflected by our finding that the pressure half times and peak velocities in our study exceeded the normal values for native valves in the mitral and tricuspid positions. A major advantage of this study was that each patient had the same type of prosthetic valve in both the mitral and tricuspid position. It was therefore possible to study the behaviour of the valve in different positions at the same examination, and thus under virtually identical haemodynamic conditions.

We found no significant difference in the pressure half time or peak velocity between the Björk-Shiley or Carpentier-Edwards valve implanted in the same valve position. However, the pressure half time range for normal tricuspid prosthetic valves was found to be considerably longer than that of mitral prosthetic valves (Björk-Shiley 50–195 ms *v* 71–120 ms and Carpentier-Edwards 38–197 ms *v* 79–110 ms respectively). This could represent functional obstruction to flow caused by the nature of the valve coupled with greater tissue ingrowth or pannus formation on the tricuspid valve. However, the tricuspid prosthesis seems to function satisfactorily even with what would be considered a very long pressure half time of 197 ms. It is worth emphasising that the dividing range between clinically normal and abnormal prosthetic tricuspid valves is small (197–237 ms). For mitral prosthetic valves a gradual increase in obstruction to flow might be expected to present earlier as dyspnoea on effort and evidence of pulmonary venous congestion. Perhaps the tricuspid valve has to be more critically obstructed before symptoms or signs are apparent. Once this critical point is reached the valve dysfunction quickly becomes apparent, possibly owing to added thrombus formation over an area of low flow. Although pressure half time is predominantly dependent on the valve area it is by no means the only factor of influence. Flow deceleration, of which pressure half time is one measure, across normal mitral and tricuspid native valves may increase with impairment of left or right ventricular diastolic function.[11 12] Patients who undergo simultaneous mitral and tricuspid valve replacement often have more severe, and less reversible, pulmonary hypertension. This could conceivably lead to right ventricular hypertrophy, impairment of right ventricular diastolic function, and misleading long pressure half times. Although there was no significant impairment of right or left ventricular systolic function on echocardiographic examination in our patients, this does not exclude some degree of abnormal diastolic function.

In our group mitral valve pressure half times showed only mild beat to beat variation, even in atrial fibrillation (0–35 ms) while there was considerable beat to beat variation across the tricuspid prosthetic valves (10–95 ms). This has been noted by other groups[5] and probably represents more considerable changes in flow and valve orifice area with respiration and varying cardiac cycle length. This emphasises the importance of taking pressure half time measurements from several cardiac cycles especially for tricuspid prosthetic valves. The peak flow velocities across both types of normal tricuspid prosthetic valve were similar, but the five obstructed tricuspid valves showed a significant increase in peak velocity, ranges 0·6–1·6 *v* 1·53–1·94 m/s respectively. Interestingly there was no significant difference in peak velocities between mitral or tricuspid prosthetic valves.

Unfortunately all flow mapping techniques with either colour flow or standard pulsed

Doppler have only a limited relation to the degree of valve regurgitation. Many of the limitations are similar to those found with contrast ventriculography—that is the size and pressure of the chamber into which regurgitant blood is flowing influence the contrast ventriculographic appearances of the regurgitant dye and also the size of the regurgitant Doppler signal. So we may have missed an eccentrically placed leaking prosthetic jet with pulsed Doppler, and metal valves can create reverberations that mask flow behind the prostheses, leading to blind spots when the transthoracic approach is used for the pulsed Doppler sampling technique. Regurgitation was more common in the group with obstructed valves but in all this was judged to be mild, and this degree of regurgitation should not have interfered with the pressure half time or peak velocity results.

We conclude that long term follow up of patients with prosthetic valves is required to assess the full role of Doppler echocardiography in detecting and measuring dysfunction of the tricuspid prosthetic valve. The normal range of pressure half times for the Björk-Shiley and Carpentier-Edwards valves in the mitral position cannot be applied to valves in the tricuspid position. The valve seems to function well with very long pressure half times and we would be cautious about diagnosing valve obstruction/dysfunction on the basis of a prolonged pressure half time or increase in peak velocity alone. However, there may be a narrow dividing line between normal and abnormal tricuspid prosthetic valves and once this is passed valve dysfunction may quickly become apparent. Our study showed that a pressure half time of >200 ms coupled with a peak velocity of $>1{\cdot}6$ m/s in the absence of severe regurgitation confirmed appreciable obstruction of the tricuspid prosthetic valve. We recommend that all patients with prosthetic valves should be examined by Doppler echocardiography soon after operation. Such a baseline characterisation of each individual's Doppler values would make serial evaluation much more meaningful.

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Changes in the pressure-volume relation of the right ventricle when its loading conditions are modified

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Abstract

Ventricular pressure-volume diagrams were obtained from the right ventricle in patients before and after relief of right ventricular pressure load, in patients with volume loaded right ventricles, and from the left ventricle in patients after the Mustard procedure for transposition of the great arteries. The patterns of ejection during pressure development and decline were similar in patients after relief of pressure load and in those with isolated volume load. A right ventricular pressure load, however, reduced ejection during the two "isovolumic" periods, and the overall shape of the pressure-volume loop resembled that of the normal left ventricle. Pressure-volume diagrams obtained from the left ventricle after the Mustard procedure were indistinguishable from the normal right ventricle, which accords with the hypothesis that the normal right ventricular contraction pattern is a consequence of loading conditions rather than a reflection of an intrinsic property of the myocardium.

The pressure-volume characteristics of the normal right ventricle were described in an earlier study.[1] Briefly, the pressure-volume loop of the normal right ventricle is more triangular than that of the left, with poorly defined periods of isovolumic contraction and relaxation and a phase of ejection during the decline in right ventricular pressure. It was suggested that these differences were load dependent and therefore reflected the different impedance characteristics of the systemic and pulmonary vascular beds. If this were the case, then large changes might be expected when the loading conditions of the right ventricle are modified. As yet there are no data on the pressure volume relation of the human right ventricle with varying loading conditions.

We studied pressure-volume loops obtained from patients with various conditions that subject the right ventricle to differing loading conditions and from the left ventricle in patients after the Mustard operation, when the left ventricle acts as the pulmonary ventricle.

Patients and methods

PATIENT GROUPS

Group 1 consisted of 16 patients (age range 1–19, median 3·5 years) with raised right ventricular systolic pressure; 10 had a diagnosis of cyanotic tetralogy of Fallot, four had valvar pulmonary stenosis, and two cor pulmonale. The mean (SD) right ventricular peak systolic pressure in this group was 58 (9) mm Hg.

Group 2 consisted of five patients with right ventricular volume load (age range 1·5–28, median 14 years). Three had an ostium secundum atrial septal defect and in two there was hemianomalous pulmonary venous drainage. Only patients with right ventricular peak systolic pressures of <35 mm Hg were included (mean 30 (6) mm Hg). The mean ratio of pulmonary to systemic flow in these patients was 2·2 (0·7) to 1.

Group 3 consisted of 10 symptom free patients studied 1–6 years after total correction of tetralogy of Fallot. Right ventricular systolic pressure in this group was 28 (7) mm Hg and no residual intracardiac shunt was detected in any patient. Nine patients had undergone enlargement of the right ventricular outflow tract with insertion of a Dacron patch. Three patients had short early diastolic murmurs in the pulmonary area suggesting the presence of pulmonary regurgitation. Transannular repair (extending the patch across the pulmonary valve annulus) was not performed in any of the patients. Some of the patients in this group and some in group 1 were included in a previous study to examine other aspects of right ventricular function after repair of tetralogy of Fallot.[2]

Group 4 included three patients (aged 9, 9, 11 years). All had undergone a Mustard repair of simple transposition of the great arteries. After this operation the right ventricle acts as the systemic ventricle and the left ejects into the pulmonary circulation. Left ventricular pressure-volume diagrams were obtained in these three patients who had normal pulmonary artery pressures and no obstruction of the left ventricular outflow tract. The left ventricular systolic pressure in this group was 26 (5) mm Hg.

METHODS

All paediatric patients were studied during general anaesthesia with (alphaxalone-alphadolone acetate, Althesin) after

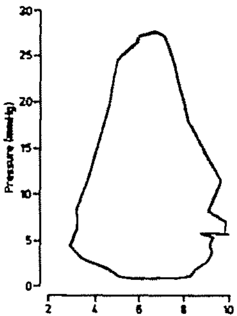


Figure 1

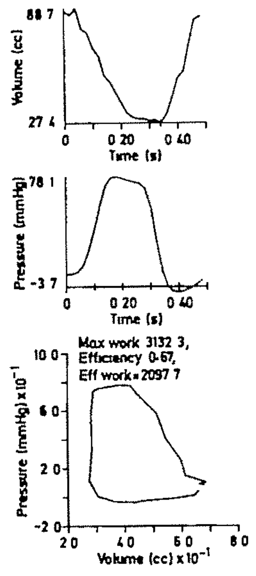


Figure 2

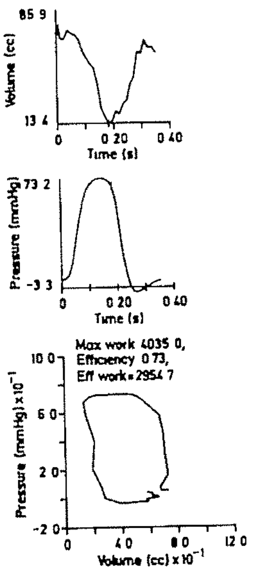


Figure 3

Figure 1 A normal right ventricular pressure-volume diagram illustrating ejection during pressure development and decline. (Taken from Redington et al, Br Heart J 1988;59:23–30, fig 4.)

Figure 3 Right ventricular pressure-volume diagram from a patient with pulmonary stenosis. There are well-defined periods of isovolumic contraction and relaxation.

Figure 2 Right ventricular pressure-volume diagram taken from a patient with tetralogy of Fallot. Ejection was occurring during pressure development but not during pressure decline. Maximum work and effective work are measured in mm Hg × ml.

premedication with trimeprazine. Adult patients were studied under local anaesthesia, without premedication. Biplane right (groups 1, 2, and 3) and single plane left (group 4) ventriculograms were recorded by the methods described previously.[1 3] When the heart rate exceeded 100 beats per minute the cineframe rate was increased from 50 to 75 frames per second. Simultaneous pressure measurements were made with micromanometer tipped catheters (Millar Instruments). The electrocardiogram, cineframe marker, and event mark were recorded to enable later synchronisation of pressure and volume data.

ANALYSIS

Only normally conducted beats were analysed; extrasystoles and immediate extrasystolic beats were excluded. Only beats recorded after the end of contrast injection were examined. Ventriculograms and pressure recordings were digitised with equipment described elsewhere.[1 2] Right ventricular volumes were corrected with the regression equations derived from cast studies.[1] Left ventricular volumes were estimated from single plane ventriculograms by the area-length method.[3]

Pressure-volume diagrams were drawn for each patient and the following measurements made:

(*a*) End diastolic volume index—that is end-diastolic volume corrected for body surface area (ml/m^2)
(*b*) Stroke volume index (ml/m^2)
(*c*) Cycle efficiency (%)
(*d*) Percentage of ejection occurring during pressure rise
(*e*) Percentage of ejection occurring during pressure fall

The derivation of these indices has been described in detail elsewhere.[1]

STATISTICAL ANALYSIS

All variables were expressed as the mean (SD). However, for the purposes of comparison, we did not assume that the variables were normally distributed and we therefore compared group data by the non-parametric Mann-Whitney U test. The null hypothesis was rejected if $p < 0{\cdot}05$.

Results

The table shows the data from all patient groups. For comparison we include our data on the normal right and left ventricle.[1 4]

RIGHT VENTRICULAR VOLUMES

These measurements were not the focus of this study and so will be described only briefly.

The end-diastolic volume index in groups 2 and 3 was higher than normal ($p < 0{\cdot}02$, $p < 0{\cdot}05$ respectively) and higher than in group 1 ($p < 0{\cdot}05$, $p < 0{\cdot}02$ respectively). The stroke volume index in the volume loaded group (group 2) was higher than normal ($p < 0{\cdot}05$), but otherwise there was no significant difference between the groups. The ejection fraction in groups 2 and 3 was lower than in the normal right ventricle (both $p < 0{\cdot}05$).

PRESSURE-VOLUME RELATIONS

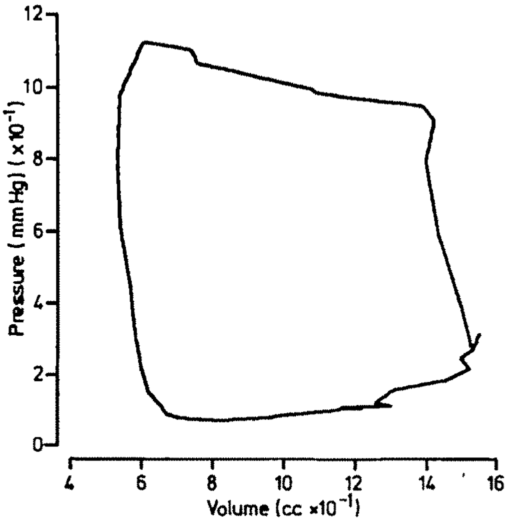
Group 1 Pressure-volume loops in patients with right ventricular pressure load were abnormal (compare fig 1 with figs 2 and 3). Their overall shape resembled that obtained from the normal left ventricle (fig 4). There was a well defined end systolic shoulder in all patients, with approximately 5% of ejection occurring during right ventricular pressure decline ($p < 0{\cdot}001$ compared with normal). In nine patients (eight with tetralogy of Fallot and one with pulmonary stenosis) there was appreciable (> 10%) ejection during the pressure rise (mean change for group = 27%, p = NS compared with the normal right ventricle). There was a significant linear relation

Data obtained from pressure-volume diagrams from each of the four study groups (mean 1SD). Data from the normal right and left ventricle are included for comparison. See text for details

	EDVI (ml/m²)	*SVI (ml/m²)*	*EF (%)*	*Ejection pressure rise (%)*	*Ejection pressure fall (%)*	*Cycle efficiency*
Group 1 (pressure load)	66 (17)	42 (13)	63 (13)	27 (19)	5 (5)	0·74 (0·07)
Group 2 (volume load)	105 (20)	55 (18)	52 (12)	18 (9)	42 (24)	0·59 (0·04)
Group 3 (relief of pressure load)	92 (30)	48·5 (16)	52 (6)	40 (8)	30 (9)	0·55 (0·01)
Group 4 (LV post-Mustard)	56 (6)	37 (4)	66 (6)	26 (8)	36 (6)	0·58 (0·06)
Normal RV	64 (13)	43 (8)	62 (6)	39 (4)	43 (9)	0·56 (0·08)
Normal LV	61 (9)	47 (9)	77 (6)	4 (5)	0	0·78 (0·08)

EDVI, end diastolic volume index· SVI, stroke volume index; EF, ejection fraction.

Figure 4 A normal left ventricular pressure-volume diagram. (Taken from Redington et al, Br Heart J 1988;59:23–30, fig 7.)



between peak right ventricular pressure and percentage ejection during the pressure rise $(r = -0\cdot65, p < 0\cdot05)$.

Group 2 The shape of the pressure-volume loops in these patients with right ventricular volume load was indistinguishable from that of the normal right ventricle. Cycle efficiency and percentage ejection during pressure fall were not significantly different from normal. In one case, however, there was no ejection from the right ventricle during pressure development (fig 5). This finding remains unexplained.

Group 3 After the relief of right ventricular outflow tract obstruction there was a tendency for right ventricular end diastolic volume to increase, but this did not reach statistical significance. The loops from these patients showed significant differences, however. Cycle efficiency was lower $(p < 0\cdot005)$ as was percentage ejection during pressure fall $(p < 0\cdot005)$. There was no difference in percentage ejection during pressure rise. None of the measured loop variables was significantly different from normal. In eight of the patients the loops also showed an increase in volume during pressure fall (fig 6). In the absence of continued injection of contrast, filling through a ventricular septal defect, or through the tricuspid valve, this volume increase during pressure decline must represent pulmonary regurgitation. The measurement and relevance of this are discussed in a previous study.[2]

Group 4 Left ventricular pressure-volume loops after the Mustard operation (fig 7) showed that 26% of ejection occurred during pressure rise and 36% during pressure fall (not significantly different from the normal right ventricle). Cycle efficiency was significantly lower than that for the normal left ventricle $(p < 0\cdot01)$ but was similar to values obtained from the normal right ventricle (p = NS).

There was no significant linear relation between any of the indices measured and heart rate in any of the groups.

Discussion

The accuracy and reproducibility of our method of measuring the volume of the normal right ventricle have already been established.[1] The regression equations used to correct the angiographic estimate of right ventricular volume were obtained from the study of human and animal casts of the right ventricle. In our validation studies we tried to maintain the normal geometry of the right ventricular casts, particularly the normal curvature of the interventricular septum. Pressure or volume loading, however, are likely to change the normal geometry. Indeed, numerous echocardiographic studies showed changes in right ventricular geometry, particularly the shape and position of the interventricular septum.[5,6] It may be incorrect, therefore, to apply these

Figure 5 Right ventricular pressure-volume diagram from a patient with a large atrial septal defect. Ventricular volumes were increased but the overall shape of the loop was similar to that of the normal right ventricle (fig 1).

Figure 6 Right ventricular pressure-volume diagram from a patient after repair of tetralogy of Fallot. Ejection was occurring during pressure development and decline.

Figure 7 Left ventricular pressure-volume diagram obtained after Mustard repair of transposition of the great arteries. The left ventricle (ejecting into the pulmonary circulation had similar pressure-volume characteristics to the normal right ventricle (fig 1).

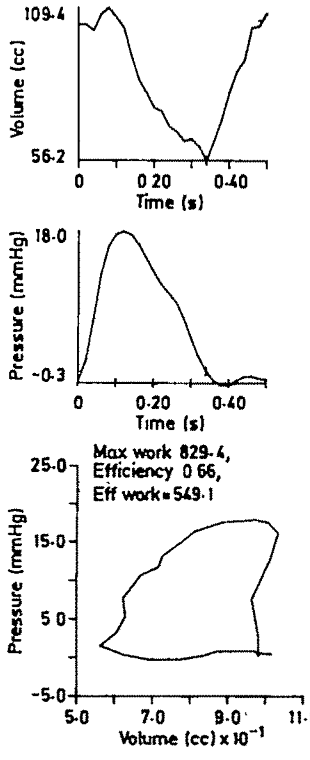


Figure 5

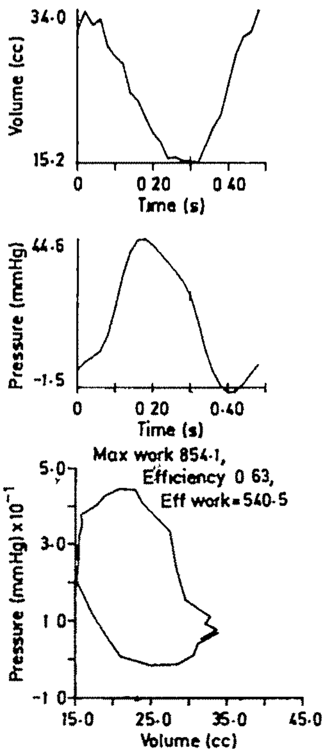


Figure 6

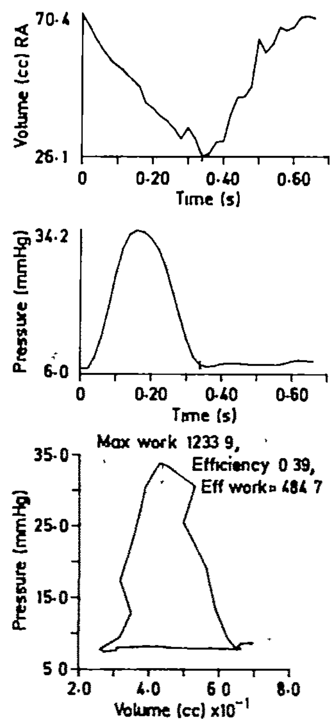


Figure 7

regression equations, as is usually done, to the estimation of right ventricular volume in patients with pressure or volume load. Ideally regression equations appropriate to the condition being studied should be obtained by studies of postmortem casts. But such studies are almost impossible to organise. Furthermore, although absolute volume measurements may be subject to error, relative changes, frame-by-frame changes throughout the cardiac cycle for example, should be valid. There was a similar problem with measuring left ventricular volume in group 4. In these patients left ventricular volumes were measured by the area-length method, a method which assumes that the shape of the left ventricle is a prolate ellipsoid. After the Mustard operation the normal pressure gradient from the left to the right ventricle is reversed and consequently the position of the interventricular septum changes. The right ventricle becomes more circular in cross section and the left ventricle seems to be "wrapped" around it.[7] Once again the use of a method that has been validated in the normal ventricle may be inappropriate when the normal geometry changes. As with the pressure and volume loaded right ventricles mentioned above, relative changes in volume (like those measured in this study) should, however, be maintained and examination of pressure-volume loops by the measurements described in this study (all of which are independent of absolute volume) should be valid. Furthermore, despite these potential errors, when groups 1, 3, and 4 (that is patients with no intracardiac shunting, and no valve regurgitation) were compared with normal individuals there was no significant difference between measurements of stroke volume, suggesting that any error introduced was small.

The aim of this study was to document any differences between the normal right ventricular pressure-volume loop and loops obtained from the right ventricle as it is affected by changes in its loading conditions. If, as was suggested previously,[1] the shape of the normal right ventricular pressure-volume loop is dependent on the low pressure, high capacitance characteristics of the pulmonary vascular bed, then large changes might be expected when these conditions change.

Group 1 consisted of patients with relative obstruction to outflow from the right ventricle. The level of obstruction varied within the group, however. It was predominantly subvalvar in those with tetralogy of Fallot, valvar in patients with pulmonary valve stenosis, and at the arteriolar level in patients with pulmonary vascular disease. Despite these differences the shape of the pressure-volume loops in these patients was remarkably consistent. In particular, the occurrence of ejection during pressure decline, which was a striking feature in the normal right ventricular pressure volume loop, was absent when there was raised right ventricular pressure. In these loops there was a period of truly "isovolumic" pressure decline. Indeed, cycle efficiency and percentage ejection occurring during pressure decline were no different from those in the normal left ventricle. One would expect from these observations that closure of the pulmonary valve would coincide with the onset of pressure decline—that is the "hangout" period, described by Shaver *et al*[8] and discussed in detail elsewhere,[1 9] should be shorter. This is indeed the case—the hangout period in the pressure-loaded right ventricle was similar to that seen in the systemic circulation.[8]

The percentage of ejection occurring during the pressure rise was not significantly different from that in the normal right ventricle of these patients, however. This cannot be explained on the basis of tricuspid regurgitation, which was not seen on the angiograms. It is possible that this finding represents early systolic shunting across the ventricular septal defect from the right to the left ventricle, but again this was not obvious from the angiograms. There was, however, a significant inverse linear relation ($r = -0{\cdot}65$, $p < 0{\cdot}05$) between right ventricular systolic pressure and the percentage of ejection occurring during the pressure rise, suggesting that this is a load dependent phenomenon. The right ventricular outflow tract obstruction in tetralogy of Fallot is often predominantly subvalvar and dynamic. The peak outflow tract gradient occurs late in systole, and so another explanation may therefore be that this phenomenon represents forward flow into the pulmonary artery, which is permitted by the relatively small outflow tract gradient during early systole. So it is interesting that eight of the 10 patients with tetralogy of Fallot but only one of the remaining six patients in this group had significant ejection during pressure development.

Right ventricular pressure-volume loops from patients with volume load and after relief of pressure load had the characteristics of the normal right ventricle. Volume loading alone, without an increase in pulmonary artery pressure, led to an increase in right ventricular volume but did not influence the pattern of ejection. Similarly after relief of outflow tract obstruction the systolic portion of the loop was similar to normal.

There seems little doubt, therefore, that the normal right ventricular pressure-volume loop reflects a series of load dependent phenomena. Some of these phenomena have been observed when the loading conditions of the left ventricle are manipulated. Ejection during pressure rise occurs when there is a low pressure "run-off", in mitral regurgitation for example,[10] and animal experiments have shown that with extreme afterload reduction much of left ventricular ejection can take place during pressure decline.[11] After the Mustard operation for transposition of the great arteries the left ventricle ejects into the pulmonary vascular bed. Thus there is a unique opportunity to examine whether the normal right ventricular pressure-volume loop is entirely dependent on its loading conditions or whether it, in addition, reflects an intrinsic property of the right ventricular myocardium. After the Mustard operation the left ventricular pressure-volume loops were indistinguishable from those of the normal right ventricle, with similar cycle efficiency and percentage ejection occurring during pressure rise and fall. In another study pressure-dimension loops obtained from unoperated patients with simple transposition of the great arteries (obtained by M mode echocardiography with simultaneous pressure measurements) showed a similar pattern.[12]

What are the clinical implications of these findings? We have previously suggested that the measurement of isovolumic and end systolic indices of right ventricular contraction may be invalid because of the lack of a truly isovolumic contraction period and the lack of adherence to the time-varying elastance (E) model of contraction, upon which end systolic indices—for example E_{max}—are based. A poorly defined period of isovolumic contraction remains a feature of the right ventricular pressure-volume loop when there is pressure load but an isovolumic relaxation phase and end systolic shoulder, likely to coincide with E_{max} (as in the left ventricle), can be defined. Measurement of E_{max} should therefore be possible for the right ventricle under these conditions. The slope of E_{max} is likely to be linear and vary with changes in inotropy, as has been observed for the canine right ventricle.[13] However, the validity of E_{max} is based on its independence from loading conditions. In this study we have shown that this is clearly not the case, either for the right or for the left ventricle. The implications are clear. The measurement of E_{max} for the pressure loaded right ventricle should be possible, but its theoretical basis is unsound, and although they are often used to assess left ventricular contractility such measurements are open to the same criticisms as above and should be interpreted with caution.

We showed that the shape of the normal right ventricular pressure-volume loop depends on its loading conditions rather than reflecting a specific property of the right ventricular myocardium. This may have important implications for the measurement of right ventricular function.

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Anomalous origin of the left coronary artery from the pulmonary trunk: elucidation with colour Doppler flow mapping

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Abstract

Four infants and children with anomalous connection of the left coronary artery to the pulmonary trunk were studied with colour Doppler flow mapping. In three the diagnosis was only suspected when the colour Doppler study showed dilated intraseptal and epicardial vessels and an abnormal flow signal into the pulmonary artery in diastole; this latter signal localised the exact site of communication, which was not apparent on angiocardiography. Two of these patients had previously had operations for severe mitral regurgitation, the diagnosis of anomalous left coronary artery having been previously considered in one but missed despite aortic root angiography. The colour study in the fourth was largely confirmatory, operation without catheterisation being undertaken on the basis of the echocardiographic images. By contrast in two infants subsequently seen with congestive cardiomyopathy the demonstration of flow direction in the left coronary artery confirmed that it was normally connected to the aorta.

Colour Doppler flow mapping can show flow direction in the left coronary artery and from the mouth of an anomalous coronary artery into the pulmonary artery, thus simplifing the diagnosis and allowing the site of the connection of the left coronary artery to the pulmonary artery to be determined with precision.

The demonstration of the origin of an anomalous left coronary artery from the pulmonary trunk with ultrasound can be difficult and surgical correction without catheterisation has only recently been reported.[1] Doppler ultrasound has the potential to show flow in or from an anomalous artery but although pulsed Doppler can show abnormal flow patterns in the pulmonary artery[2] this is of limited value. Colour Doppler flow mapping will better show the site and direction of flow in or from a coronary artery in relation to the echocardiographic image, and should thus resolve diagnostic difficulties in doubtful cases.

We report on the findings with colour Doppler flow mapping in the assessment of four patients with anomalous connection of the left coronary artery to the pulmonary trunk, with particular reference to its value in providing information additional to that obtained with imaging ultrasound and angiography. In addition, we report the Doppler ultrasound appearances of the coronary arteries in two infants with congestive cardiomyopathy examined after the benefits of the technique in such patients became apparent.

Patients and methods

Imaging and Doppler studies were performed using a Vingmed CFM 700 system. A routine M mode and cross sectional study was performed and when the diagnosis of anomalous connection of the left coronary artery was suspected or considered the echocardiographic investigation was directed to the demonstration of the left coronary artery. The colour Doppler was used to show the direction of flow in the left coronary artery or its main branches and to show flow from the anomalous artery into the pulmonary artery. The presence of flow signals in dilated epicardial and intraseptal collateral vessels was also sought.

The origin of the left coronary artery may be confused with the transverse sinus in the short axis view of the great arteries.[3] To avoid this mistake the distal part of the artery should be sought by tilting the transducer inferiorly towards the left ventricular outflow tract. In this view more of the proximal part of the artery (probably the anterior descending) may be shown passing anteriorly. With a normal connection of the left coronary artery to the aorta the flow in this artery will be towards the transducer (red in fig 1).

Results

Four patients with anomalous connection of the left coronary artery have been diagnosed since the introduction of colour Doppler flow mapping to our unit in January 1987. One was diagnosed in infancy (2 months) and the others were aged 3, 6, and 7 years. Cardiac catheterisation was performed in two, and surgical reimplantation of the anomalous coronary artery in three, including one without catheterisation.

Two infants with congestive cardiomyopathy were subsequently seen and the diagnosis of an anomalous left coronary artery

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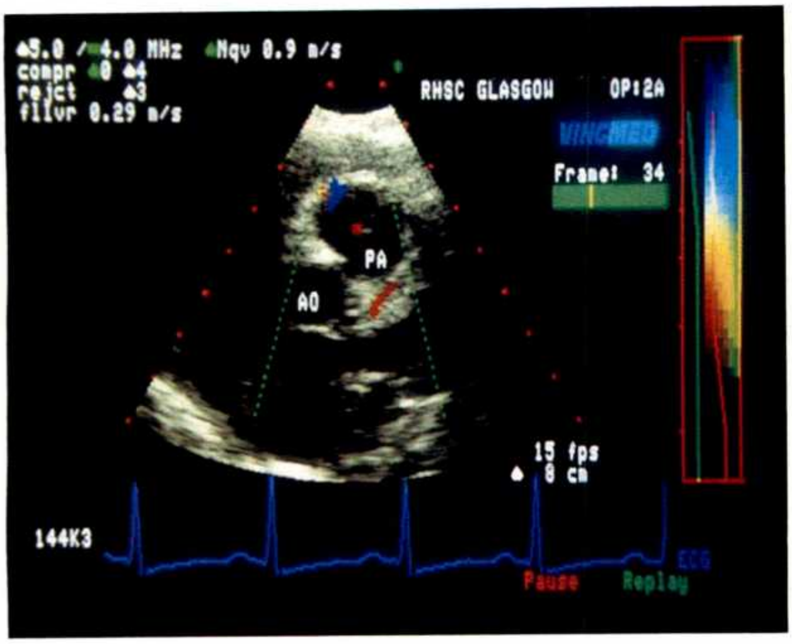


Figure 1 Colour Doppler flow mapping of modified short axis view of the great arteries in an infant with congestive cardiomyopathy showing the left main coronary artery lying behind the pulmonary artery. The ultrasound system displays flow away from the transducer as blue and towards it as red to orange. The red linear flow signal in the left coronary artery indicates flow towards the transducer. Flow is from the origin towards the bifurcation—that is, normal flow direction.

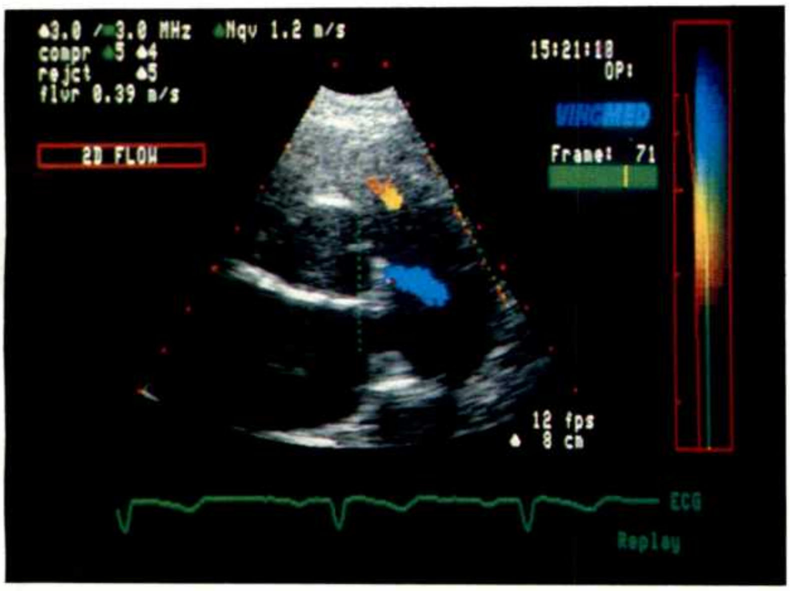


Figure 2 Colour Doppler flow mapping of short axis view of great artery origins in diastole showing flow from the anomalous coronary into the pulmonary artery (blue) just distal to the valve sinuses and insignificant pulmonary regurgitation (orange).

was considered but not confirmed. Catheterisation was undertaken in one who also had tuberous sclerosis with mitral regurgitation.

ANOMALOUS LEFT CORONARY ARTERY: NO PREVIOUS OPERATION

Two patients had clinical signs of mitral regurgitation. The first was found to have an asymptomatic murmur at 6 years of age with the electrocardiogram showing left ventricular hypertrophy but no ischaemic changes. The second presented at the age of 8 weeks with cardiac failure and ischaemic changes on the electrocardiogram. In both, echocardiography showed a dilated left ventricle with decreased contractility, affecting the posterior wall more than the septum. There were bright echoes from the papillary muscles, particularly the lateral one. An image of the aortic root initially suggested that the left coronary artery arose from the aorta, but that there was an enlarged right coronary in the infant. Spectral and colour Doppler confirmed the presence of mitral regurgitation.

Patient 1

In the first patient, the child of 6, the diagnosis was not suspected clinically but routine colour study of the pulmonary artery showed flow from a discrete position in the medial wall just distal to the valve sinus into the centre of the vessel, most apparent in diastole (fig 2). In this view a circular echo free space was then apparent at the point of origin of the flow and adjustment of the scanning plane showed this to be an artery with flow from it into the pulmonary artery. When this artery was traced medially it was shown that although it lay in close apposition to the aorta it did not enter it, and an image could be obtained showing the artery and the structure initially thought to be the coronary artery but presumed to be the transverse sinus.[3] In addition, the colour images of the septum and ventricular walls showed striking and abnormal flow signals (similar to those in fig 4 described below) resulting from flow in dilated collateral vessels.

Patient 2

In the second case, the infant, the diagnosis was suspected on the basis of the clinical signs and the initial electrocardiographic and echocardiographic studies. A colour Doppler flow mapping study of the pulmonary artery again showed flow into the main pulmonary artery similar to that in fig 2. More detailed echocardiographic studies showed an artery arising from the pulmonary artery and bifurcating; colour Doppler flow mapping showed that the flow was from the two branches into the main one (fig 3) and thus from the coronary artery into the pulmonary artery. Flow in the epicardial and septal vessels was not shown, presumably because the collaterals were not developed at this young age.

In the older child catheterisation provided confirmatory images of the lesion before surgical reimplantation, which was undertaken without catheterisation in the infant.

ANOMALOUS LEFT CORONARY ARTERY: PREVIOUS MITRAL VALVE SURGERY

Two children who had undergone mitral valve repair or replacement at the ages of 6 months and 2 years were reassessed 3 and 5 years after operation.

Patient 3

One girl presented with cardiac failure and was diagnosed by angiocardiography as having endocardial fibroelastosis at the age of 4 months, but at 23 months severe mitral regurgitation with apparently improved function was diagnosed. The possibility of an anomalous coronary artery was considered but aortic root angiography was interpreted as

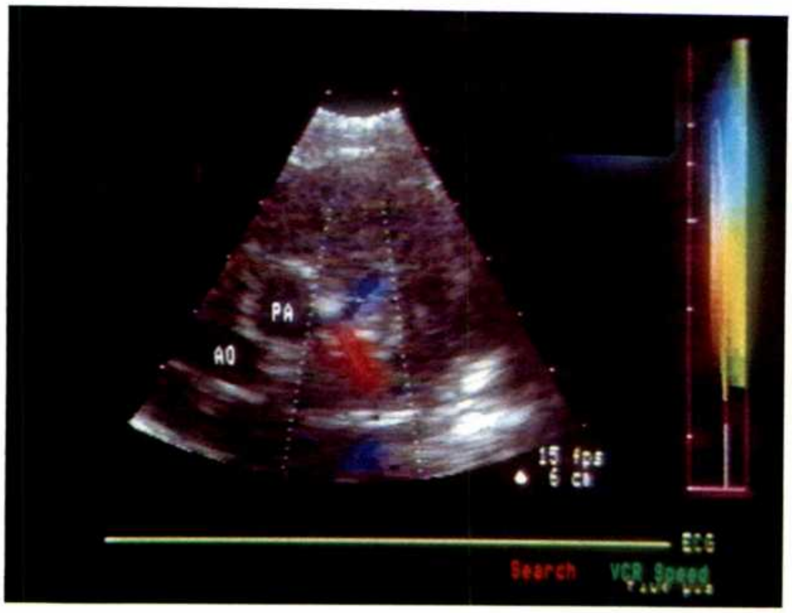


Figure 3 Colour Doppler flow mapping of still frame from video recording showing a high parasternal view of the pulmonary artery adjusted to show the anomalous vessel with flow (blue and red) from its branches towards the left main coronary artery.

showing normal right and left coronaries. After mitral valve annuloplasty at 2 years 3 months her condition improved considerably. At 8 years old she was symptom free. An ultrasound study performed to assess ventricular and mitral valve function showed satisfactory ventricular function and minimal regurgitation.

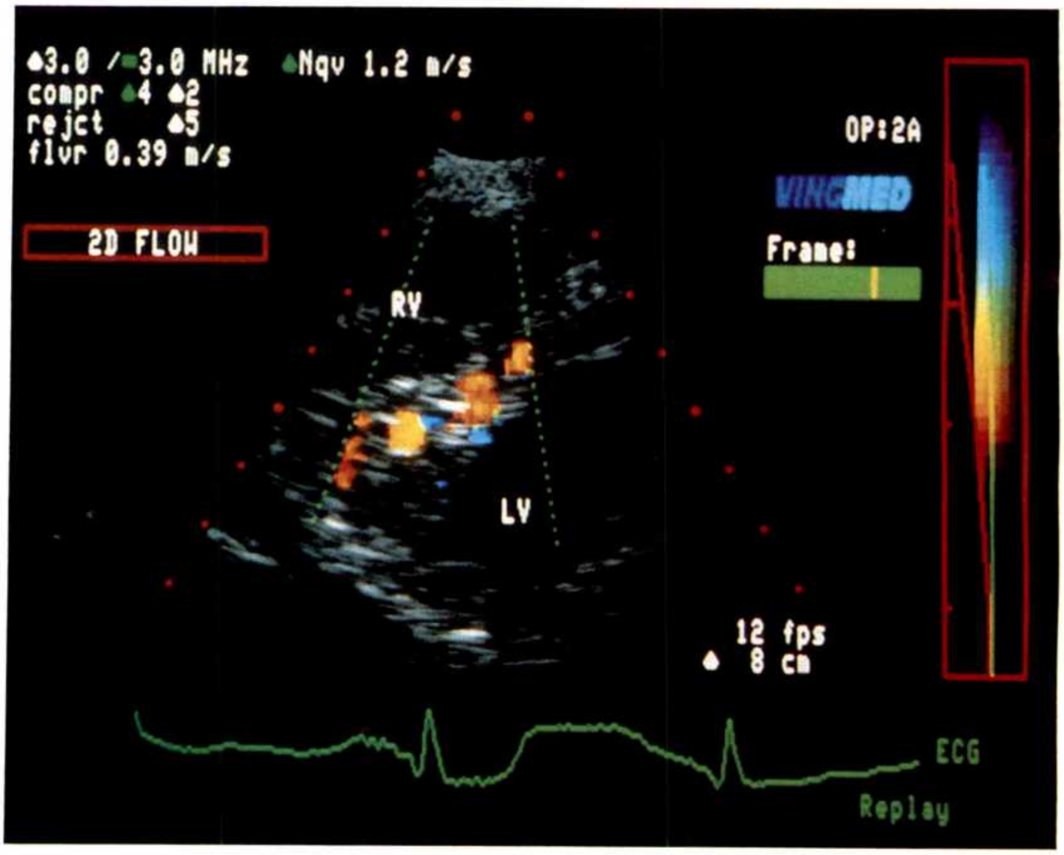
The colour Doppler flow mapping study showed prominent flow signals in the septum (fig 4) and ventricular walls; these were considered to be in dilated intraseptal and epicardial vessels respectively. Study of the origins of the great arteries then showed a flow signal that was most clear in diastole passing into the right pulmonary artery just at the bifurcation. The coronaries were then examined in detail and showed a large right coronary artery but no left coronary artery arising from the aortic root. There was also a dilated vessel with flow from it into the right pulmonary artery just distal to the bifurcation (fig 5). Subsequent right coronary angiography confirmed that there was an anomalous left coronary artery arising from the pulmonary artery, but its exact point of origin could not be ascertained. At operation the anomalous artery was found to arise from the proximal right pulmonary artery as had been shown by Doppler examination. Subsequent review of her original echocardiographic studies showed increased echogenicity of the lateral papillary muscle and a large right coronary.

Patient 4

The other patient presented at 5 months with cardiac failure and signs of mitral regurgitation. The electrocardiogram showed evidence of biventricular hypertrophy without ischaemia. Ventriculography confirmed severe mitral regurgitation and an aortic root injection was not performed. Valve replacement was undertaken and produced considerable clinical improvement. On review at 3 years he was well and the electrocardiogram showed evidence of borderline left ventricular hypertrophy but no ST changes. Colour Doppler showed dilated collateral vessels and flow into the pulmonary artery from an anomalous coronary artery.

Subsequent review of his original echocardiographic studies showed an increase in the echogenicity of the papillary muscles, particularly the lateral. He has not yet undergone surgical reimplantation.

Figure 4 Colour Doppler flow mapping of modified short axis view through the ventricles showing the ventricular septum with flow (orange) in the dilated collateral vessels in the myocardium of the septum. LV, left ventricle; RV, right ventricle.



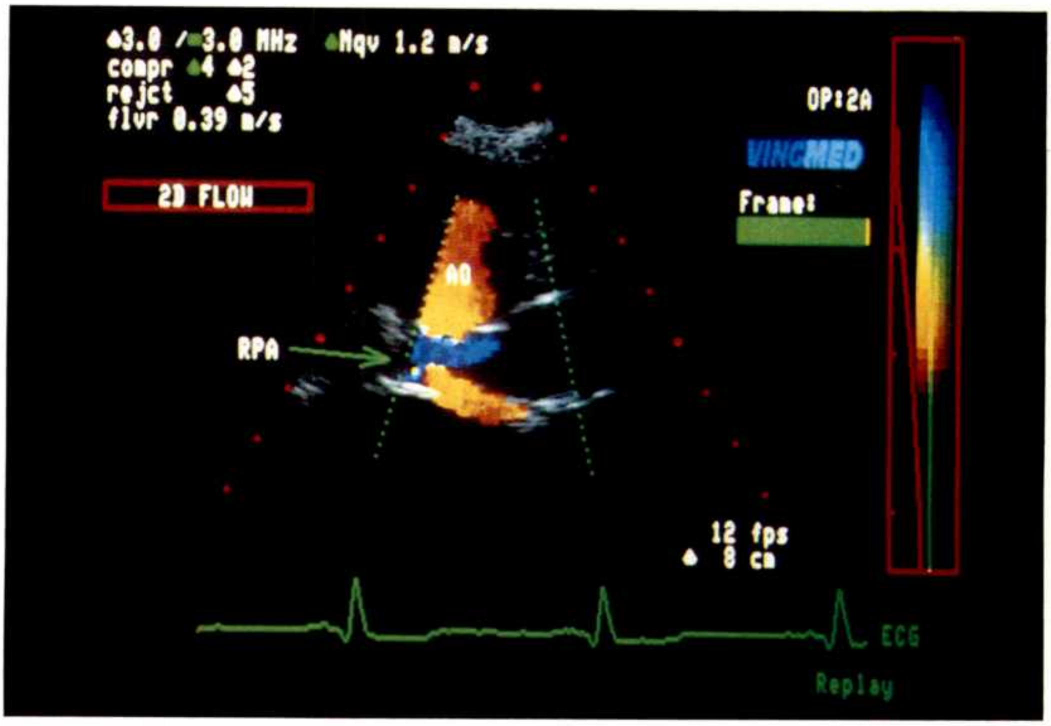


Figure 5 Colour Doppler flow mapping of short axis view of great artery origins in diastole showing flow from the anomalous coronary into the pulmonary artery (orange). Note that the signal and thus the artery origin is into the right pulmonary artery (RPA) just distal to the bifurcation, different from that in figure 2. Flow in the aorta (AO) is also coded in orange.

CONGESTIVE CARDIOMYOPATHY: NORMAL LEFT CORONARY ARTERY

Patient 5

An 8 month infant presented with cardiac failure, and left ventricular hypertrophy but little ischaemia on electrocardiography. Echocardiography showed a dilated and symmetrically poorly contracting left ventricle and colour Doppler showed no abnormal flow signals. Short axis views of the great arteries showed an apparently normal origin of the left coronary artery. When the scanning plane was tilted inferiorly as previously described, the anterior extension of this artery was apparent. Colour Doppler showed flow in this artery towards the transducer (fig 1) and thus from the aorta towards the distal aspect of this artery, representing a normal connection.

Patient 6

In a 2 week infant presenting with cardiac failure echocardiography showed intramyocardial tumours suggesting the diagnosis of tuberous sclerosis which was confirmed by Wood's light examination. Initial response to medical treatment was not continued and she became worse with mitral regurgitation and cardiac failure. Echocardiographic examination suggested normal origin of the coronary arteries and colour Doppler showed a normal direction of flow in the artery, thus confirming the assessment.

Discussion

Anomalous origin of a coronary artery from the pulmonary trunk is a relatively uncommon lesion. Aortic root angiography can be inconclusive[4] and the lesion may not be diagnosed without a selective injection into the right coronary artery.

It is not sufficient to find that the origin of a coronary artery from the aorta cannot be shown by echocardiography; it may be that the origin has been missed. In addition, the transverse sinus of the pericardium has been mistaken for an aortic origin of the left coronary artery.[3] Very rarely there can be origin of the circumflex and right coronary arteries from the aorta with the anterior descending arising directly from the pulmonary artery.[5] The presence of a dilated right coronary artery is helpful in distinguishing the lesion from dilated cardiomyopathy[6] but is not diagnostic and can be found in other defects. Furthermore, although an abnormal artery may be seen it was reported some years ago that it was not always possible with imaging ultrasound to trace it into the pulmonary artery.[7] Modern imaging systems make the recognition more simple but although repair on the basis of the echocardiographic image after inconclusive angiography has been reported[8] we are aware of only one previous report of repair without catheterisation.[1]

We consider that if the left coronary artery seems to arise from the aorta the scanning plane must be adjusted to show its distal course, and colour flow mapping should be used to determine whether the direction of flow is normal as in fig 1 or abnormal as in fig 3. If modern high quality imaging and colour Doppler systems are used there should be little difficulty in determining the origin and direction of flow in the left coronary artery in infants but this may be less easy in older patients. Although the flow direction will vary with the pulmonary artery pressure, this is likely to be retrograde by the time signs and symptoms of anomalous left coronary artery become apparent.

It is noteworthy that the cross sectional study in all four patients with an anomalous left coronary artery showed very bright echoes from the papillary muscles, presumably the result of ischaemic damage, which also resulted in mitral regurgitation. It thus seems that brightness of the papillary muscles and a dilated right coronary artery should alert the examiner to the possibility of an anomalous left coronary artery if this was not previously suspected.

In the three patients in whom the diagnosis was not suspected clinically it was only suggested from the unusual flow signal in the pulmonary artery (fig 2) or dilated myocardial and epicardial collaterals vessels. The possibility of an anomalous left coronary artery in patients with the primary clinical feature of mitral regurgitation has been highlighted by Noren *et al.*[8] The appearance of flow in the collateral vessels is very striking and should alert the examiner to the possibility of the diagnosis; it is not clear at what age this becomes apparent but it is not likely in the early months before good collateral arteries have developed. The flow direction in the septal and anterior and posterior epicardial vessels was away from the transducer when it was in the subcostal and apical positions, indicating flow from the right coronary towards the anterior descending and circumflex coronary arteries. In the rare situation of anomalous origin of the anterior descending coronary artery colour Doppler should show flow into the pulmonary artery. It is to be expected that flow will be in the same direction in the septal and anterior epicardial collateral vessels but in the opposite direction (towards the transducer) in the posterior epicardial ones. This should facilitate the assessment of this condition which is otherwise very difficult to recognise.

The site of connection of the anomalous coronary to the pulmonary artery is usually just distal to the pulmonary valve[9] but this is not always the case (see patient 3) and angiography may not show its exact position. It can then be difficult for the surgeon to locate it, and colour Doppler provides the ideal means to demonstrate clearly the site of the origin.

We consider that colour Doppler flow mapping used with good imaging is the most appropriate ultrasound means for establishing the diagnosis of anomalous origin of the left coronary artery from the pulmonary artery. The clarity of this demonstration, by adding greatly to the other echocardiographic findings, will allow surgical repair without recourse to catheterisation in many patients. It provides a unique means to ascertain the exact site of origin of the anomalous artery and thus assists the surgeon in the technical approach to the procedure.

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CASE REPORTS

Treatment of a malignant bronchial carcinoid affecting the mediastinum and left atrium by radical two stage resection with cardiopulmonary bypass and somatostatin infusion

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Abstract

At operation a malignant bronchial carcinoid that had invaded the left atrium produced a carcinoid crisis in a 63 year old woman. A somatostatin infusion was required to resuscitate the heart and circulation and to allow subsequent resection of the carcinoid under cardiopulmonary bypass.

The malignant carcinoid syndrome has excited clinical interest and posed a therapeutic challenge since its description 30 years ago. The disorder is usually associated with carcinoid tumours of the small bowel that are metastatic to the liver. It may less often be seen in association with primary carcinoid in other sites such as the lung or stomach or, more rarely, with non-carcinoid tumours such as small cell carcinoma of the lung. Bronchial carcinoids are of fore-gut origin unlike the more commonly found ileal tumours which are of mid-gut origin. Fore-gut carcinoids usually do not possess the decarboxylase enzyme required for generation of serotonin (5-HT) from its precursor 5-hydroxytryptophan.[1] Therefore 5-hydroxyindole acetic acid, which is usually present in the urine as a marker of the carcinoid syndrome, will often not be found. Peripheral conversion of precursor to serotonin can often occur in the liver, intestine, and kidney. Methyldopa may also block the decarboxylase enzyme.

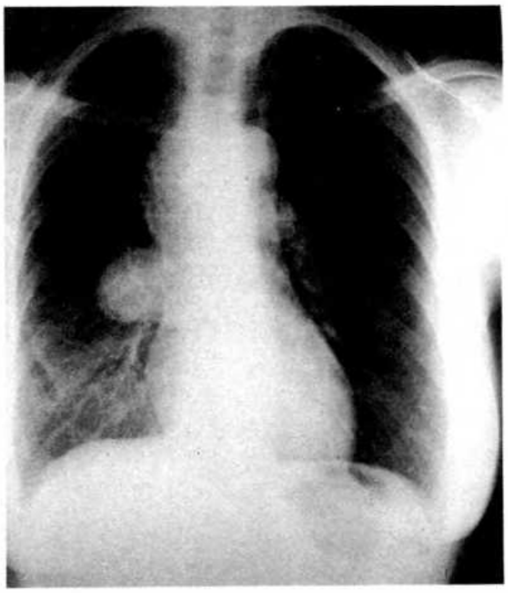
Bronchial carcinoid tumours rarely cause symptoms though "atypical" pulmonary carcinoids with more aggressive cell type and clinical behaviour have been recognised.[2] Radical surgical excision is recommended for these tumours.[3] We describe a patient with a primary lesion which directly invaded the left atrium and with a large solitary metastasis in the posterior mediastinum. A two stage approach was required for excision.

Case report

A 63 year old white female non-smoker presented with a nine month history of persistent distressing cough. For a month she had also had epigastric pain and flushing of the face. She was not taking methyldopa. There had been no diarrhoea or weight loss or other features of the carcinoid syndrome. Physical examination showed no abnormality. There were no cardiac murmurs. A chest radiograph (figure) showed a 5 cm diameter mass at the right hilum with a further large paratracheal mass in the mediastinum above the azygos vein. A computerised tomogram suggested that this was a solitary enlarged lymph gland. A provisional diagnosis of bronchogenic carcinoma was made based on these findings.

Bronchoscopy, with the rigid Stortz scope, showed external compression of the lateral wall of the right bronchus intermedius and of the right tracheal wall but no intraluminal tumour. Mediastinoscopy was performed to obtain a histological diagnosis. The smooth tumour was easily located and a biopsy specimen was taken without event. Histology showed this to be a metastatic bronchial carcinoid; however, despite a history suggestive of hormone secretion, urinary hydroxyindole acetic acid estimations proved negative. Biochemical and haematological screening tests were normal. Liver ultrasound and bone scans were unremarkable.

Because there was no evidence of extrathoracic spread surgical resection was considered to be the treatment of choice. The first approach was by right thoracotomy which confirmed the preoperative findings. The mediastinal deposit measuring 10 cm by 8 cm was first mobilised and then excised without difficulty from the mediastinum. No other signs of tumour spread were seen and there were no adverse haemodynamic consequences. However, the pulmonary mass was situated centrally, between the superior and inferior pulmonary veins and seemed to invade through the pericardium at this point. Involvement of the hilum including the right main pulmonary artery above the fissure meant that pneumonectomy was required. However, an attempt to mobilise the lesion provoked profound hypotension (systolic <30 mm Hg) and there was no response to transfusion or massive doses of adrenaline. Interestingly, there was no concomitant tachycardia. The tumour was highly



Posterior-anterior chest radiograph showing the right hilar bronchial carcinoid primary and azygos nodal metastasis.

vascular and invaded directly into the cavity of the left atrium. At this stage we did not have somatostatin; this was obtained some 30 minutes later. During this time the blood pressure remained below 50 mm Hg and the operation was abandoned despite persistent bleeding. An intravenous bolus (250 μg) of somatostatin increased the blood pressure immediately to normal (140/90 mm Hg). A continuous infusion of 250 μg/h was started but because the tumour secretion was so high supplies of somatostatin were exhausted in two hours and the blood pressure again fell to 30 mm Hg. The patient remained moribund for a further two hours despite transfusion of 6 l of blood and intravenous hydrocortisone. When further supplies of somatostatin were obtained, blood pressure again returned to normal and she made a satisfactory recovery in the intensive care unit. 5 Hydroxyindole acetic acid estimations were repeated but were again negative.

Three days later she returned to the operating room for right pneumonectomy. A somatostatin infusion was started at a rate of 250 μg/h before anaesthesia and was maintained throughout the operation. Median sternotomy was performed and a clotted right haemothorax was evacuated. Cardiopulmonary bypass was established before the tumour was touched. Exploration of the lung hilum confirmed that the tumour invaded directly into the cavity of the left atrium between the pulmonary veins. Pneumonectomy was performed with excision of the wall of the left atrium. This provided good tumour clearance. The mitral valve seemed normal and there was no haemodynamic instability. Perfusion pressure during cardiopulmonary bypass was 60–70 mm Hg. The defect was closed by direct suture and cardiopulmonary bypass was discontinued without difficulty. Somatostatin infusion was stopped eight hours after operation and the patient made a satisfactory recovery.

Histology of the primary lesion confirmed that it was an "atypical" carcinoid tumour, though the hormone was not identified. Eighteen months after the operation the patient remains well.

Discussion

Two types of carcinoid tumour are recognised by histology and by clinical behaviour. So called "typical" carcinoid has a characteristic histological appearance and patients with this tumour have a five year survival in excess of 80%. "Atypical" carcinoids (10–20% of all bronchial carcinoids) show greater mitotic activity, nuclear atypia, and metastasis to lymph nodes. Five year survival when node involvement is found at presentation is only 25%.[2 4]

The diagnosis of carcinoid syndrome, with primary bronchial carcinoids, usually requires either extensive intrathoracic spread or hepatic secondary deposits. The patient described had neither but the tumour was able to secrete directly into the cavity of the left atrium and systemic circulation. The bronchial carcinoid syndrome has a characteristic pattern. The flush is prolonged, up to 24 hours, and may affect the entire body; there may be lacrimation, hypotension, periorbital oedema, and facial and salivary gland swelling.[1] The absence of 5-hydroxyindole acetic acid in the urine should not have surprised us because these tumours commonly lack the decarboxylase enzyme to convert precursor (5-HTP) to serotonin. More than twenty different mediators have been recognised and in our patient the clinical findings were more in keeping with the release of bradykinin, histamine, or substance P. Indeed, substance P has been shown to be 100 times more potent a vasodilator than bradykinin and it causes flushing, bradycardia, and hypotension.[5] Direct secretion of such a substance into the left atrium avoids the usual detoxifying action of liver or lung found with carcinoids at other sites.

Somatostatin, discovered in hypothalamic tissue 13 years ago, is a naturally occurring hormone with pronounced inhibitory effects on the secretion of many endogenous peptides such as growth hormone, insulin, glucagon, and gastrointestinal peptides. Native somatostatin has been reported to be effective in blocking the carcinoid flush induced by pentagastrin, in reducing circulating concentrations of serotonin, and in controlling other symptoms associated with the carcinoid syndrome. However, it has a limited therapeutic application because its short half life necessitates continuous intravenous infusion. Hypertensive crises can also occur during anaesthesia in patients with carcinoid tumours that secrete serotonin. Somatostatin was reported to reverse a potentially lethal carcinoid crisis during induction of anaesthesia.[6] Certainly in our patient somatostatin dramatically and repeatedly reversed circulatory collapse in a carcinoid crisis in which 5-hydroxyindole acetic acid was not found. Excision of the tumour with cardiopulmonary bypass would have been impossible without continuous somatostatin infusion because sudden profound vasodilatation would have emptied the bypass circuit and brought the extracorporeal circuit to a halt. The circulation was completely unaffected by adrenaline infusion during the carcinoid crisis.

Recently a somatostatin analogue, SMS 201-995 (Sandoz, East Hanover, NJ) was used on a long term basis by subcutaneous injection to control symptoms of the carcinoid syndrome.[7] It has been associated with decreased concentrations of urinary 5-hydroxyindole acetic acid and with regression of hepatic metastases. It is apparent that somatostatin or its analogue should be available when operations are undertaken in patients with the carcinoid syndrome whether or not this is positive for hydroxyindole acetic acid.

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Reversible impairment of myocardial function in hypoparathyroidism causing hypocalcaemia

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Abstract

A 25 year old woman presented with severe myocardial dysfunction. Laboratory tests showed hypocalcaemia caused by hypoparathyroidism. After the restoration of normal concentrations of serum total and free ionic calcium indices of left ventricular function returned to normal and her symptoms disappeared.

The important role of calcium ions in the contraction of cardiac muscle fibres is well known.[1] None the less, there are few reports of well documented cases in which hypocalcaemia caused reversible myocardial dysfunction.[2–4] We describe a patient in whom cardiac failure with a prolongation of the QT interval, cramps,[5] and convulsions was caused by hypocalcaemia. Hormone assay showed hypoparathyroidism.

Case report

A 25 year old woman was first admitted to our department with a history of pulmonary oedema and congestive heart failure, which had been treated successfully in a district hospital. When we first examined her in 1983 there was no sign of heart failure. The heart sounds were normal. Acquired and congenital heart diseases were excluded. Haemodynamic examination showed that the left ventricular end diastolic pressure was 10 mm Hg and the left ventricular end diastolic volume was 170 ml. The cardiac index was 4·1 l/m^2. The QT interval was within normal limits. The patient said that she drank about half a litre of spirits every day.

We diagnosed an alcoholic myocardial lesion; the patient's condition improved when she stopped drinking. The patient was monitored by echocardiography in the subsequent months and it seemed that she had been cured. She did not need any medical treatment.

In April 1985 she had generalised convulsions and was treated with antiepileptic drugs. But this did not stop the convulsions. Subsequently alopecia developed and her finger nails became ridged. She was admitted for a second time in November 1985. She was grey and pale. Both Chvostek's and Trousseau's signs were present and she had temporary episodes of unconsciousness with convulsions.

Her history did not include operations on the thyroid gland. The heart rate was 80 beats/minute and the systemic arterial blood pressure was 110/70 mm Hg. The liver was enlarged by 6 cm and there was mild oedema in the feet. The chest *x* ray showed a cardiac enlargement and evidence of severe pulmonary congestion. The QT interval was 0·64 s with negative T waves in leads I and V5–6 (fig 1). The echocardiogram showed left ventricular dilatation (end diastolic diameter 67 mm, end systolic diameter 58 mm). The ejection fraction was 17% by radionuclide ventriculography with technetium-99m. The carotid angiogram, isotopic brain scintigram, electroencephalogram, and skull and bone radiology were normal. Ophthalmological examination showed peripheral (mainly subcapsular) cataracts in the lenses which accorded with hypoparathyroidism. The erythrocyte sedimentation rate was 45 mm/hour and a complete blood count and urine analysis were normal. Serum concentrations of glucose, sodium, potassium, urea nitrogen, creatinine, haptoglobin, bilirubin, aspartate aminotransferase, alanine aminotransferase, glutamyltransferase, alkaline phosphatase, acid phosphatase, iron, total iron binding capacity, total protein, and albumin were normal. The Coombs, Kürten, latex, and lupus erythematosus tests were negative. The table shows the concentrations of serum total and free ionic calcium, magnesium, and inorganic phosphate on admission and before discharge.

Concentrations of hormone (with methods of measurements and normal ranges in brackets) were as follows: urine 17-hydroxycorticosteroids 3·9 mg/24 hour (Porter-Silber colorimetry, 1·8–6·0 mg/24 h); 17-kerosteroids 7·3 mg/24 h (Zimmermann colorimetry, 5·0–15·0 mg/24 h); serum cortisol 431 nmol/l (fluorimetry, 221–550 nmol/l); testosterone 1·88 nmol/l (radioimmunoassay (RIA), 0·86–

Data on admission and before discharge

Variable	*On admission*	*Before discharge*	*Range*
Total serum calcium (mmol/l)	0·53	1·98	1·90–2·50
Free ionic calcium (mmol/l)	0·32	1·24	0·95–1·25
Inorganic phosphate (mmol/l)	3·25	1·67	1·00–1·70
Tubular phosphate resorption (%)	95–99	71·8	65–90
Magnesium (mmol/l)	0·63	0·98	0·50–1·00

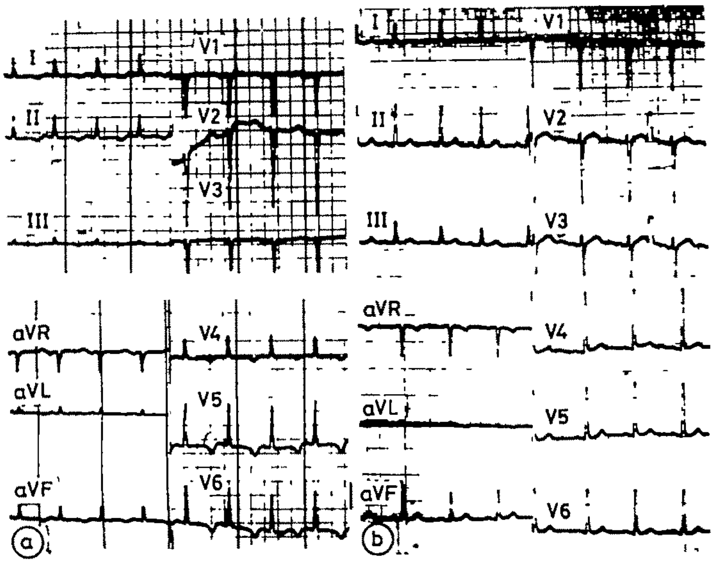

Figure 1 12 lead electrocardiogram on admission (a) and before discharge (b). The QT interval was initially 0·64 s. After restoration of the serum calcium it was 0·38 s. The heart rate was essentially unchanged.

2·77 nmol/l); calcitonin 8 pmol/l (RIA Mallinckrodt kit, 0–44 pmol/l); parathormone 21·06 pmol/l (RIA Mallinckrodt kit, 15–60 pmol/l). The parathormone was almost undetectable. No further decrease in serum parathormone concentration was detected after intravenous administration of calcium. The typical clinical signs, the long QT interval, the increased tubular phosphate resorption, and the low serum concentration of parathormone were consistent with extreme hypocalcaemia and led to a diagnosis of hypoparathyroidism caused by a parathormone deficiency. Alcohol induced hypomagnesaemia may also have contributed to the impairment of parathormone release. We treated the patient with intravenous calcium and dihydrotachysterol drops. Shortly afterwards the cramps disappeared; they have not recurred.

Figure 2 shows the changes in the serum total and free ionic calcium and inorganic phosphate, and also the left ventricular ejection fraction, fractional shortening, end diastolic diameter, and the effect on corrected QT interval. Serum concentrations of total and free ionic calcium correlated strongly with the left ventricular variables. These variables gradually increased during treatment, while the serum inorganic phosphate and corrected QT interval decreased to normal. Between days 50 and 60, a dihydrotachysterol and calcium overdose produced high concentrations of calcium and a low concentration of phosphate. Later, an optimum regimen of oral calcium and dihydrotachysterol was attained. Since then the patient has remained well. She takes 500 mg calcium three times a day and 12 drops of dihydrotachysterol. Tubular phosphate resorption and other variables have returned to normal (table).

Our patient had a sister who died of congestive heart failure at the age of 16. Congenital and acquired valve diseases were excluded. There was no satisfactory explanation for her death.

Discussion

Although free ionic calcium has a well defined role in myocardial contractility, there are few well documented reports of the association of hypocalcaemia and disturbances of myocardial contractility. Giles *et al* reviewed seven published case reports and presented an additional one of "reversible congestive cardiomyopathy": all of these patients had hypoparathyroidism and impaired myocardial function.[2] These cases suggested the role of hypo-

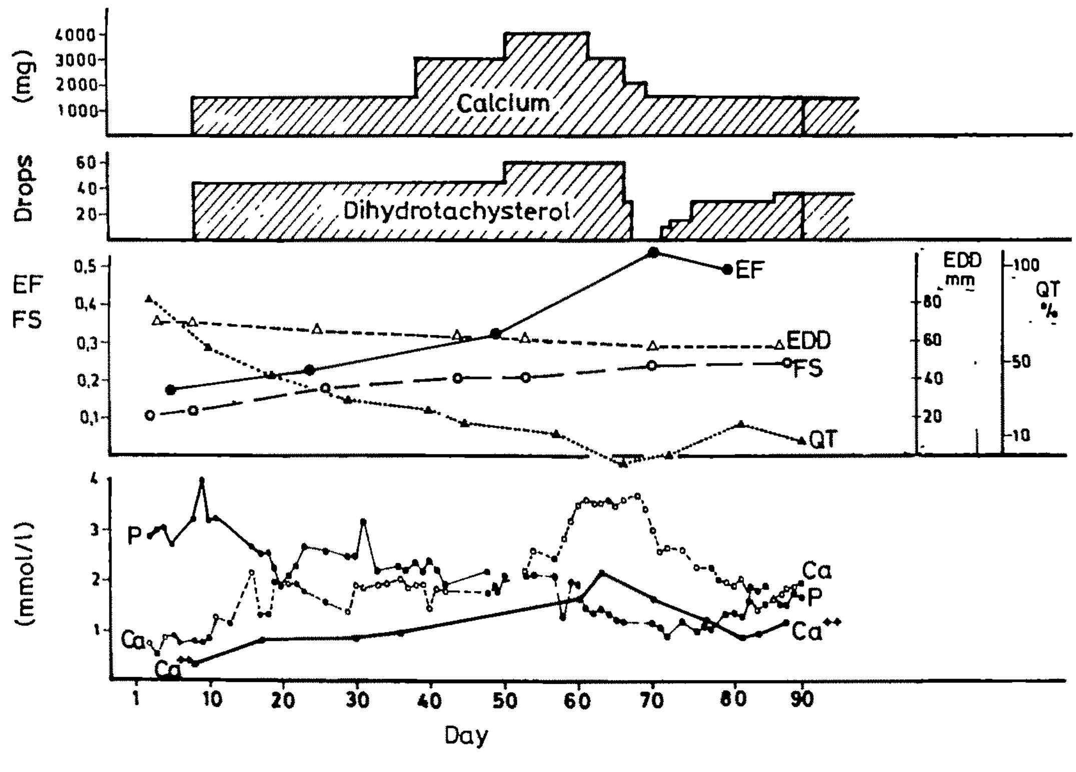

Figure 2 Treatment regimen, indices of left ventricular function, and the change in QT interval, serum concentrations of total calcium and free ionic calcium, and the serum concentration of inorganic phosphate. EF, ejection fraction; EDD, end diastolic diameter; FS, fractional shortening. The percentage difference between the measured and ideal QT intervals was calculated.

calcaemia and hypomagnesaemia in the development of congestive heart failure in hypoparathyroidism, but they did not establish causal relations. In 1983, Ginsburg *et al* reported the case of a boy with severe congestive heart failure who had a low serum concentration of free ionic calcium.[3] After this was restored to normal his myocardial contractility improved. They reported a direct relation between the serum concentration of free ionic calcium and myocardial performance. Connor *et al* reported a case in which hypocalcaemia precipitated congestive heart failure, and restoration of the normal serum concentration of calcium produced a clinical recovery but they did not monitor left ventricular function.[4] Our data confirmed that an increase in serum calcium (the total and free ionic calcium concentrations moved in parallel) caused an improvement in left ventricular function.

The unexpected death of a young sister of our patient owing to congestive heart failure suggests the possibility of the familial occurrence of congestive heart failure precipitated by hypocalcaemia.[6] Our case report shows that hypocalcaemia can cause reversible disturbances of myocardial contractility that resemble congestive cardiomyopathy.

We thank Dr István Marz (Railway Hospital, Budapest), Dr Tamás Janáky (Endocrinology Unit, Szeged), Dr István Móczó (2nd Department of Medicine, Szeged), and Dr Tibor Szabó (Nuclear Medicine Department, Debrecen) for their help

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Intrapericardial bleomycin for the management of cardiac tamponade secondary to malignant pericardial effusion

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Abstract

A patient with malignant pericardial effusion with cardiac tamponade was treated by the instillation of intrapericardial bleomycin. The tumour deposits elsewhere in the body continued to progress and eventually killed the patient, but drainage and one dose of intrapericardial bleomycin prevented further episodes of pericardial effusion.

Malignant pericardial effusions are said to be responsible for one third of cases of cardiac tamponade.[1] This condition often presents as a medical emergency, though it can present gradually with progression of signs over several hours, or indeed days. The situation is usually life threatening and prompt adequate treatment is essential. Percutaneous drainage of the pericardial effusion produces instant relief of the signs and symptoms and instillation of various substances, including antibiotics (tetracycline) and chemotherapeutic agents (nitrogen mustard, thiotepa, mepacrine hydrochloride) have been used with varying degrees of success. Bleomycin is less often used in this condition but is efficacious. We describe a patient in whom intrapericardial bleomycin provided useful palliation, although the tumour was unresponsive to systemic chemotherapy.

Case report

A 53 year old man was admitted to the hospital with a seven day history of dyspnoea on exertion and left sided chest pain. Examination showed a regular tachycardia of 120 per minute, pulsus paradoxus, a raised jugular venous pressure, a blood pressure of 110/70 mm Hg, and an enlarged lymph gland in the left posterior triangle of his neck. There was a moderate left sided effusion. Chest *x* ray showed a large heart with clear margins, a mass eroding the right third rib, and confirmed the left sided pleural effusion (fig 1a). The echocardiogram confirmed a large pericardial effusion (fig 1b). Cytological examination of the pleural fluid showed adenocarcinoma cells. Over the next 24 hours the patient's condition deteriorated with symptoms of dizziness and increasing breathlessness, a rise in the pulse rate to 150 per minute, and a fall in systemic blood pressure to 100/60 mm Hg. At this stage we placed a percutaneous catheter in the pericardial sac using a Seldinger technique and drained 800 ml of heavily bloodstained fluid. This produced prompt relief of the symptoms and improved his signs. Adenocarcinoma cells were found in the pericardial fluid.

Free drainage of the pericardial space via the catheter continued for four days, then 5 mg of bleomycin in 20 ml of water was instilled into the pericardial sac. The catheter

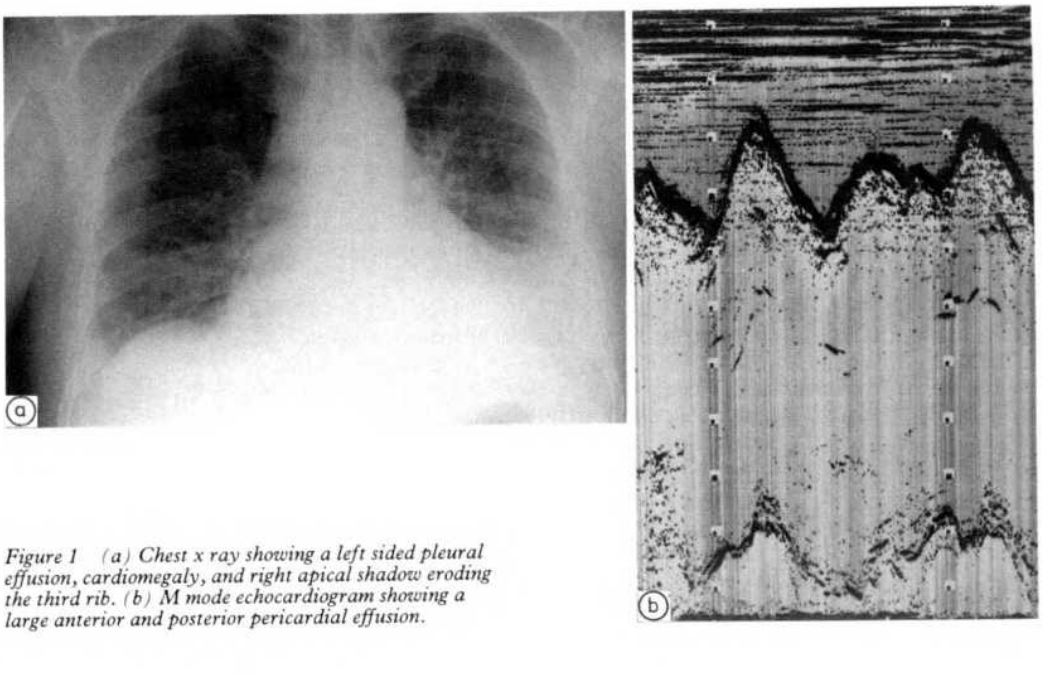

Figure 1 (a) Chest x ray showing a left sided pleural effusion, cardiomegaly, and right apical shadow eroding the third rib. (b) M mode echocardiogram showing a large anterior and posterior pericardial effusion.

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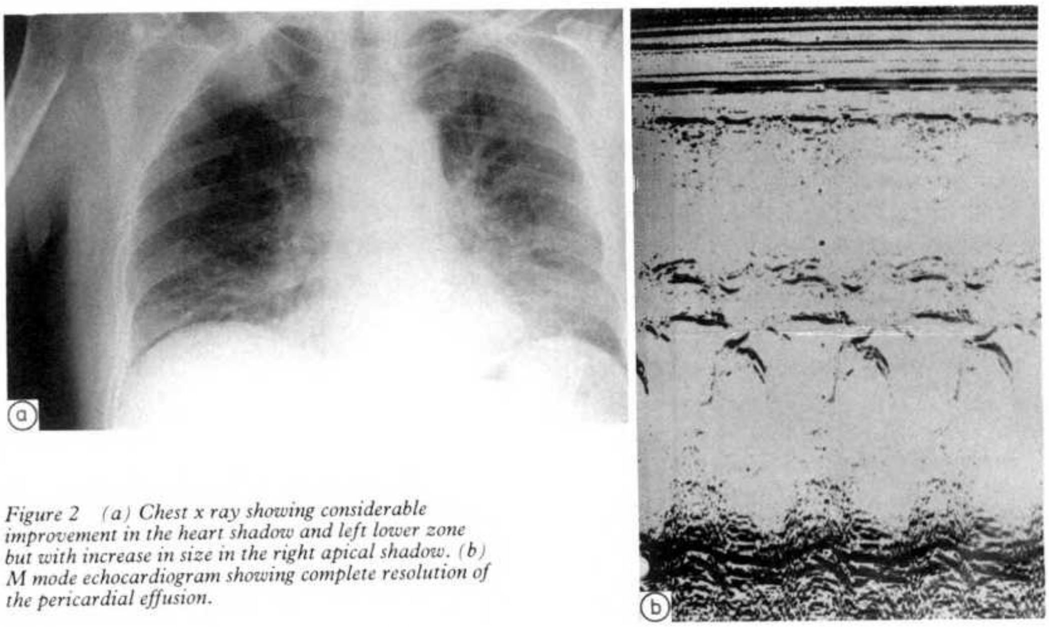

Figure 2 (a) Chest x ray showing considerable improvement in the heart shadow and left lower zone but with increase in size in the right apical shadow. (b) M mode echocardiogram showing complete resolution of the pericardial effusion.

was then clamped and removed 24 hours later. No adverse effects were seen with this procedure, either during the acute period or afterwards. However, the chest pain that was present on admission persisted. Despite an extensive search for the underlying primary site, we found no evidence of tumours in the kidney, gastrointestinal system, bronchus, or pancreas.

We thought that the tumour was probably pulmonary in origin. Despite the low response rate of lung adenocarcinomas to chemotherapy, we believed that it was appropriate to give this man a trial of combination chemotherapy. He was started on monthly courses of 24 hour treatment with ifosfamide, etoposide, vincristine, and mesna. Despite continued tumour growth at other sites (including the neck, a right sided mass on chest *x* ray (fig 2a), recurrence of pleural effusion, and subsequently cerebral metastases), there was no clinical, radiological, or echocardiographic evidence of recurrence of the pericardial effusion (fig 2b) from the time of the initial diagnosis up to death 65 days after presentation.

Discussion

It is better to use conservative measures rather than operation to treat cardiac tamponade secondary to malignant pericarditis.[2] Agents that are instilled into the pericardial space include nitrogen mustard,[2] radioactive gold,[3] 5-fluorouracil,[4] tetracycline,[5] and bleomycin.[6–8] At present, the least toxic drugs for treatment of malignant effusions are tetracycline and bleomycin.[9 10] These are equally effective.[11] There are, however, no comparative data on the treatment of pericardial effusion. Published reports suggest that pyrexia and pain may be more common after the use of tetracycline.[6 9]

Bleomycine is toxic at doses of $40\ mg/m^2$ much in excess of that required for control of pericardial effusion. We know of eight reported cases of the use of intrapericardial instillation of bleomycin. In six there was no recurrence of effusion up to the time of death and one patient survived for 434 days. The effusion recurred 14 days after treatment in one patient and at 2·5 months in another. No recurrence of effusion was noted after pericardial instillation of tetracycline in six patients.[6] Tetracycline and bleomycin seem to be equally effective but we believe that more information on treatment failures and adverse reactions is required to clarify the role of these agents in the treatment of this uncommon disorder.

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Arterial microembolisation: an unusual presentation of dilated cardiomyopathy

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Abstract

Systemic embolisation is common in patients with dilated cardiomyopathy. Microembolisation as a presenting sign of dilated cardiomyopathy, however, has not been reported before. A 37 year old woman in whom dilated cardiomyopathy presented as arterial microembolisation to the toes is described.

Dilated cardiomyopathy is a clinical syndrome characterised by ventricular dilatation and associated systolic dysfunction in the absence of pericardial, valvar, or coronary artery disease.[1] The clinical presentation, course, and prognosis of dilated cardiomyopathy are highly variable. In most studies of the clinical presentation of dilated cardiomyopathy, embolism was identified as a frequent and serious complication of this disease.[2] It is estimated that at least 11% of patients with dilated cardiomyopathy have one or more embolic events during the course of their illness.[3] The timing and severity of thromboembolism in patients with dilated cardiomyopathy are highly variable. In some instances embolic events are clinically silent and are detected only at necropsy as peripheral infarcts in patients dying of progressive congestive heart failure. More commonly, embolism occurs long after the onset of clinical evidence of congestive heart failure.[4] In a few patients embolic events precede all other cardiac symptoms and the clinical effects of peripheral infarcts may overshadow the primary cardiac disease and confuse the diagnosis. Retrospective evaluation of these patients, however, has generally shown that radiographic cardiomegaly or electrocardiographic abnormalities were present at the time of embolisation.[4 5]

The systemic emboli described in patients with dilated cardiomyopathy are generally large and affect, in order of decreasing frequency, the lungs, the kidneys, the spleen, and the brain.[6–10] The occurrence of arterial microemboli as a presenting feature of dilated cardiomyopathy has not been reported before. We describe a patient in whom arterial microembolisation was the presenting sign of dilated cardiomyopathy.

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Case report

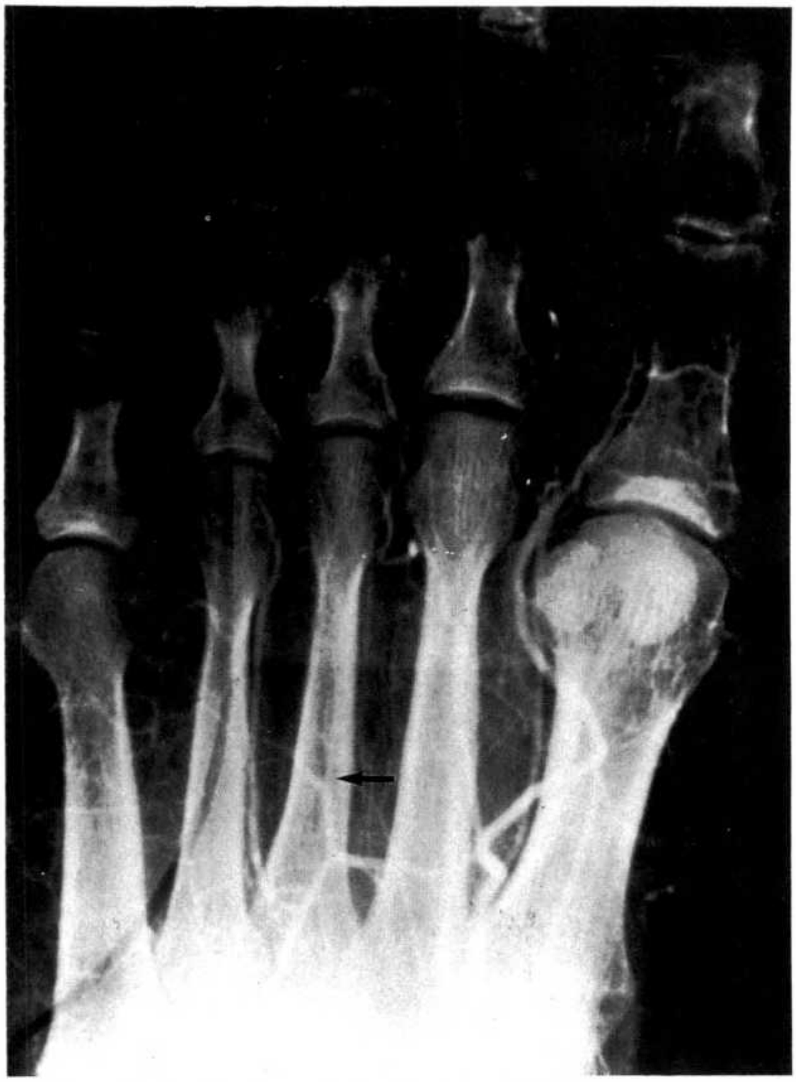
A 37 year old white woman was admitted to the hospital with severe pain and discoloration in both fifth toes. She had been in good health until a month before admission when she noticed a painless "bluish discolouration" of the left fifth toe followed by similar changes in the right fifth toe. Two weeks before admission she had severe intermittent pain in both discoloured toes particularly at night. The pain was improved by walking and was partially relieved by analgesics. The pain was not exacerbated by exposure to cold. The patient did not report any symptoms of congestive heart failure including exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and peripheral oedema. The patient had no history of arthritis or cerebrovascular disease. No history of rash, or symptoms attributable to a coagulation disorder, connective tissue disease, or vasculitis were elicited. There was nothing relevant in the patient's family history. The patient had consumed two ounces of vodka daily since the age of 18 and had smoked 40 cigarettes a day for 15 years.

PHYSICAL EXAMINATION

Examination showed: blood pressure 110/68 mm Hg, pulse 80 beats/min, respiration 16 breaths/min, and temperature 36·5°C. Fundoscopic examination did not show retinal haemorrhages, exudates, or other vascular abnormalities. Heart sounds were normal but there was a soft systolic ejection murmur along the left sternal border. The abdominal examination was entirely normal. The right and left fifth toes were cool, cyanotic, and exquisitely tender. Peripheral pulses were within normal limits. Both affected toes showed increased sensitivity to pin prick but the neurological examination was otherwise normal.

Blood chemistry values were normal. Complete blood count was normal except for a raised mean corpuscular volume of 112 fl. Prothrombin and partial thromboplastin times were normal. The erythrocyte sedimentation rate was 11 mm/h (Westergren). Antinuclear antibody, rheumatoid factor, and cryoglobulins were not detected. Antithrombin 3, protein C, and complement concentrations were normal.

The electrocardiogram showed T wave inversion in the inferior and precordial leads. The chest *x* ray showed slight enlargement of the cardiac silhouette. An aortogram and arteriogram of the toes were performed from the femoral approach. This showed occlusion of the digital arteries supplying the left fifth and third toes (figure). There was partial revascularisation from a collateral circulation. There was no angiographic evidence of atherosclerosis or vasculitis in the aorta or more



Arteriogram of the left foot showing complete occlusion of the digital arteries supplying the left fifth and third (arrow) toes.

distal vessels. M mode and cross sectional echocardiography showed left ventricular enlargement, diffuse hypokinesis, and an apical mural thrombus. Radionuclide ventriculography showed a reduced left ventricular ejection fraction of 35%, left ventricular enlargement, and global hypokinesis. Coronary angiography did not show luminal narrowing in the coronary arteries.

Because decreased left ventricular function could not be explained by coronary artery disease, right ventricular endomyocardial biopsy was performed to identify or rule out other myocardial abnormalities. Microscopy of the myocardial biopsy samples showed myofibre hypertrophy and increased interstitial fibrosis but no evidence of interstitial inflammatory infiltrates or myocyte necrosis consistent with the diagnosis of myocarditis. The small intramyocardial blood vessels seen in the endomyocardial biopsy samples were normal. The patient was treated with warfarin. The pain and cyanosis in the toes resolved within two months. The patient's cardiac function, monitored with serial physical examinations and radionuclide ventriculograms, improved progressively. A radionuclide ventriculogram performed nineteen months after the initial presentation showed a left ventricular ejection fraction of 42% and the disappearance of wall motion abnormalities. During the follow up period the patient did not drink any alcohol but she was unable to stop smoking.

Discussion

We report an unusual presentation of dilated cardiomyopathy in which systemic arterial microemboli preceded the symptoms and signs of congestive heart failure. Emboli to the lungs, kidneys, spleen, and brain are known to complicate the course of dilated cardiomyopathy and in some patients to precede all other cardiac symptoms.[4 5] Kyrle *et al* reported that peripheral embolisation complicates dilated cardiomyopathy.[11] In this series, however, peripheral emboli occurred in patients with known cardiac dysfunction and were not the presenting sign that led to the diagnosis of dilated cardiomyopathy.

Ischaemia of the toes may be caused by peripheral vascular diseases including atherosclerosis, Buerger's disease, small vessel disease associated with diabetes mellitus, vasculitis, and microemboli. Angiography is helpful in identifying or ruling out these possibilities. In our case there were no angiographic changes of atherosclerosis, Buerger's disease, or vasculitis of large or medium sized arteries. Abrupt occlusion of the digital arteries was seen. This picture is compatible with embolisation, a vasculitis limited to the small arteries, or diabetic vascular disease. Vasculitis was believed to be an unlikely diagnosis because there were no constitutional symptoms to suggest a systemic inflammatory process. Nor did the laboratory data including a normal erythrocyte sedimentation rate, haemoglobin, and albumin, suggest an inflammatory vasculopathy. There were no other symptoms or signs to suggest a connective tissue disease and all serological testing was negative. The presence of diabetes mellitus was excluded by the absence of symptoms and retinal changes attributable to this disease and by the finding of a normal fasting blood glucose. By exclusion of other causes, embolisation was considered the most likely explanation for the digital artery occlusions.

The left ventricular mural thrombus seen on the cross sectional echocardiogram was the only identifiable source of the patient's microemboli.

The hypothesis that emboli originate from mural thrombi that form in the cardiac chambers as the result of blood stasis secondary to severely impaired systolic function is supported by the necropsy finding of cardiac thrombi in as many as 53% of patients with dilated cardiomyopathy.[12] Other investigators have proposed that at least some embolic events in dilated cardiomyopathy are the manifestation of a generalised thrombotic tendency. This is suggested by a Japanese study of 36 patients with dilated cardiomyopathy. Four of these patients were young, suffered embolic events early in the course of their cardiac disease, which dominated the clinical picture, and died within a year of the onset of heart failure.[13] Although a hypercoagulable state could not be conclusively ruled out in our patient, the normal platelet count and normal coagulation studies make the possibility of a generalised thrombotic tendency unlikely. Another possible cause of embolism in patients with dilated cardiomyopathy is arrhythmia.[7] Our patient was in normal sinus rhythm and she had no electrocardiographic evidence of intermittent atrial fibrillation or complex ventricular arrhythmias.

Some investigators reported significant alterations in the activity of mitochondrial enzymes in the myocardial biopsy samples of patients with a history of excessive alcohol intake.[14] On the basis of this finding it has been suggested that enzyme analysis of the biopsy samples may distinguish heart failure owing to alcohol from other causes of dilated cardiomyopathy. Biochemical analysis of the myocardial tissue was not performed in our patient. Three aspects of our patient's clinical picture, however, suggest that an unusual reaction to alcohol may have contributed to her cardiac dysfunction. These include a history of alcohol intake, the raised mean corpuscular volume, and the improvement of left ventricular function after she stopped drinking alcohol. Reversal of alcoholic cardiomyopathy has been previously reported by several investigators.[15–17] Recent experimental evidence suggests that alcohol, by altering major regulatory mechanisms in the cell, has a direct toxic effect on the myocardium.[18 19] Thus it is possible that removal of the toxic insult improves cardiac function.

Another reversible cause of dilated cardiomyopathy is myocarditis.[19] Myocardial inflammation was not seen on the patient's endomyocardial biopsy samples and she had no prodromes attributable to a viral infection. But because the diagnostic value of an endomyocardial biopsy specimen is limited by the possibility of sampling error, spontaneous resolution of myocarditis cannot be excluded in our patient.[20]

Peripheral microemboli originating from a cardiac mural thrombus can be the presenting symptom of dilated cardiomyopathy. Thus this disease entity should be identified or ruled out in patients showing evidence of peripheral microembolisation even when there are no symptoms of congestive heart failure.

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Br Heart J 1990;63:66–8

Pulmonary arterial occlusions and aneurysms: a forme fruste of Behçet's or Hughes-Stovin syndrome

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Abstract

A patient is reported with pulmonary arterial occlusions and aneurysms and recurrent haemoptysis. He gave a history of recurrent arthropathy and febrile illnesses; though he had had no other features of Behçet's or Hughes-Stovin syndrome his disease probably fell into this broad diagnostic category.

Thrombotic occlusions and aneurysms of pulmonary arteries occur in Behçet's syndrome and in the closely related Hughes-Stovin syndrome. In the patient reported here, similar lesions occurred though he did not fulfil the criteria for the diagnosis of either of these syndromes.

Case report

A 27 year old Iraqi, resident in Turkey, was well until 1986 when he had an intermittently swollen right knee for six months. Later in 1986 a right pleural effusion developed; this was thought to be infective and was treated with antibiotics. Two months later he had a febrile illness thought to be a chest infection and was again treated with antibiotics. In 1987 he had fever and recurrent haemoptysis and was treated with rifampicin and streptomycin for eight months for suspected tuberculosis. Recurrent haemoptysis continued, with one major episode requiring transfusion. In February 1988, a scalene lymph node biopsy, bronchoscopy and biopsy, and mediastinotomy and biopsy gave no diagnostic information. In May 1988 he had a computed tomographic scan of the chest and pulmonary arteriogram (digital subtraction analysis).

In December 1988 he was examined at our hospital. He complained of breathlessness, but had had no haemoptysis for two months. There was no other relevant past medical history, in particular no history of orogenital ulceration, ocular or cutaneous lesions, or venous thrombosis in the legs. He had smoked 20 cigarettes a day until two years before, drank no alcohol, and had lost weight during his illness.

On examination he looked well but was thin. He was afebrile, with pulse rate of 80 per minute in sinus rhythm, and blood pressure was 130/60 mm Hg. The venous pressure was normal with no oedema; there was a widely split S_2 but no other abnormal cardiac signs. The chest was clinically clear.

INVESTIGATIONS

The electrocardiogram was normal. A chest *x* ray showed a normal sized heart and a round opacity 2 cm in diameter above and behind a prominent left hilum. There was bilateral basal pleural thickening with some elevation of the left diaphragm (fig 1).

A full blood count showed evidence of mild iron deficiency anaemia (haemoglobin 117 g/l). The erythrocyte sedimentation rate was 18 mm in one hour. Routine biochemical investigations gave normal results. A routine clotting screen and haemoglobin electrophoresis were normal. Urinalysis was normal. An autoantibody screen (including double stranded DNA antibodies) was negative, as were the Venereal Disease Reference Laboratory test and the haemagglutination tests for *Treponema pallidum*, and tests for hepatitis B surface antigen, rheumatoid factor, anti-cardiolipin antibodies, and anti-neutrophil cytoplasmic antibodies. Protein C concentration was 54% of normal, protein S 110%, and the antithrombin III concentration was 96% of normal.

The computed tomogram performed in Turkey showed enlarged hilar lymph nodes and confirmed the chest *x* ray findings.

The digital subtraction angiogram also performed in May 1988 showed multiple pulmonary arterial aneurysms of the right lower lobe pulmonary artery, left pulmonary artery at the hilum, and in the left mid-zone. There was decreased pulmonary vascularity in the left lower zone and right middle zone (fig 2a).

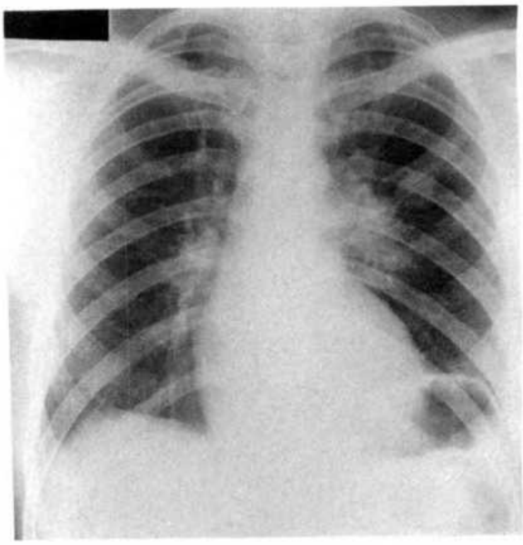

Figure 1 Chest radiograph (posterior-anterior projection).

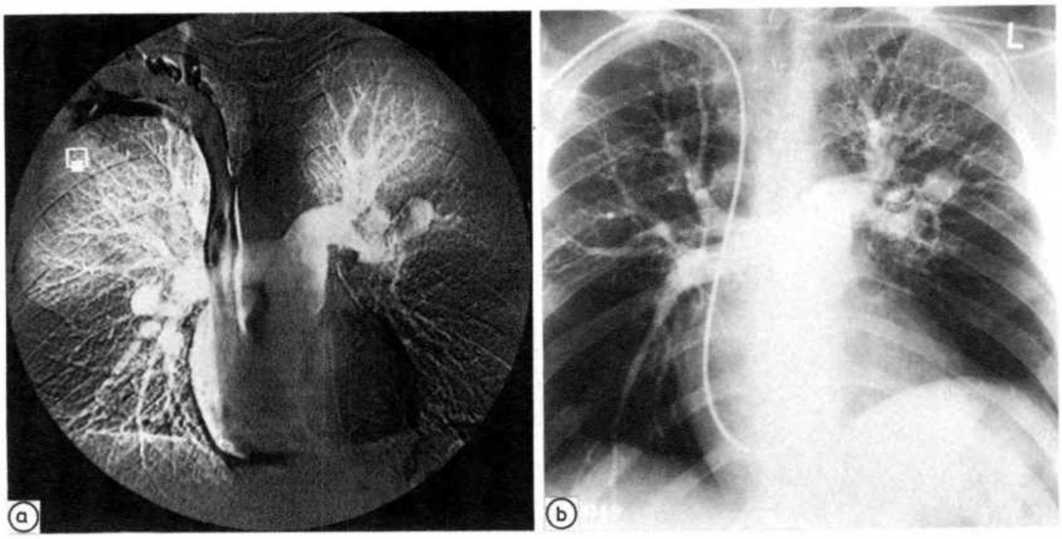

Figure 2 Pulmonary arteriograms in (a) May 1988 (digital subtraction analysis) and (b) December 1988.

Pulmonary arteriography performed at the Brompton Hospital in December 1988 showed an occluded left lower lobe pulmonary artery, occlusions of most vessels to the right lower lobe, and a single 2 cm aneurysm in the left mid-zone (fig 2b). The pulmonary artery pressure was raised (43/10, mean 25 mm Hg) and arterial oxygen saturation was 96%.

Lung function tests showed normal lung volumes with a low transfer factor. On formal exercise testing he achieved a maximum oxygen uptake of 1678 ml/min (52% of predicted normal). Though resting blood gases were normal, desaturation occurred on exercise (Pao$_2$ 8·25 kPa, saturation 90%); a high resting alveolar-arterial gradient increased during exercise. There was an abnormal heart rate response and an abnormal ventilatory response to exercise.

After these investigations the patient decided to return to Turkey and has been lost to follow up.

Discussion

Pulmonary artery aneurysms are uncommon in thromboembolic disease but do occur in association with Behçet's disease.[1-3] This is a systemic disease of unknown aetiology, which is thought to be a vasculitis,[1,4] with an unusual geographical distribution, mainly in Japan, the Mediterranean, and the Middle East.[5] The major criteria for the diagnosis are orogenital ulceration, ocular and cutaneous lesions, and thrombophlebitis[5]; none of which was present in this patient. Minor criteria include arthropathy, which he had had. In 1959 Hughes and Stovin described a syndrome of pulmonary artery aneurysms and thrombotic occlusions in association with systemic venous thrombosis.[6] Since then several more cases have been described,[7-9] mainly in young men, with haemoptysis a prominent and often fatal feature.[6,8,9] Venous occlusion is also common in Behçet's disease,[1,4] and in view of the clinical and radiological similarities between the two syndromes it has been suggested that they may have a similar pathogenesis.[3,10] Because our patient did not have a clinical history of previous systemic venous thrombosis this was not a case of classic Hughes-Stovin syndrome, but the pulmonary features and the history of systemic illness suggest that his disease falls within the same group of disorders.

Only one of the aneurysms shown on the digital subtraction pulmonary angiogram in May 1988 was evident on the pulmonary arteriogram obtained seven months later. It seems likely that there had been thrombosis of the feeding arteries during the intervening period. Recurrent or progressive vascular occlusions had resulted in increasing breathlessness and desaturation on exercise and could lead to irreversible pulmonary hypertension or respiratory failure, if haemoptysis does not prove fatal.

Steroids alone or with an immunosuppressant have been suggested as the first line of treatment,[1,11] but because so few cases have been reported no controlled trials have been performed. These agents are not always effective in preventing an unfavourable course even if some regression of aneurysms does occur.[10] Treatment with anticoagulants is potentially dangerous in view of the frequency of haemoptysis as a cause of death in both pulmonary Behçet's[1-3] and the Hughes-Stovin syndrome.[6,9] This clearly contrasts with the management of the usual forms of pulmonary thromboembolic disease.

Though most patients with Behçet's or Hughes-Stovin syndrome present to pulmonary physicians or rheumatologists, it is important for cardiologists to be aware of the pulmonary vascular manifestations of these syndromes, particularly when classic extrapulmonary features of either syndrome are absent, as in this patient.

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3 Grenier P, Bletry O, Cornud F, Godeau P, Nahum H. Pulmonary involvement in Behçet disease. *Am J Roentgenol* 1981;**137**:565–69.

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5 Lehner T, Barnes CG, eds. *Recent advances in Behçet's disease.* Royal Society of Medicine Services. International Congress and Symposium Series No 103. London: Royal Society of Medicine: 1986.

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8 Teplick JG, Haskin ME, Nedwich A. The Hughes-Stovin syndrome. Case report. *Radiology* 1974;**113**:607–8.

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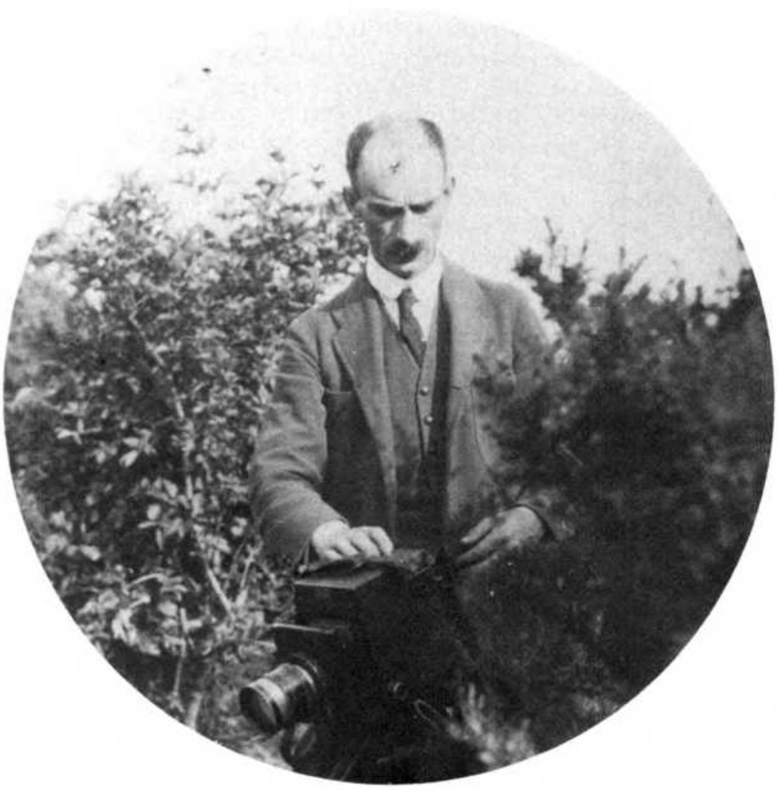
11 Cadman EC, Lundberg WB, Mitchell MS. Pulmonary manifestations in Behçet's syndrome. *Arch Intern Med* 1976;**136**:944–7.

VIEWS FROM THE PAST *Thomas Lewis 1918*



The recent happy discovery of two collections of historic photographs enables us to publish some pictures of the personalities who have contributed to the development of cardiology. Some of the members of the Cardiac Club were keen photographers; indeed Sir Thomas Lewis (1881–1945), its first chairman, was a dedicated bird-watcher from early in his career. We are grateful to Professor J D Hay of Liverpool for the loan of an extensive collection of glass slides taken over a 20 year period by his father, John Hay (1873–1959), one of the founders of the Cardiac Club. In addition (after the death last year of Sir Thomas Lewis's widow) Dr Arthur Hollman was given a number of pictures, mainly of portraits of colleagues and friends of Lewis. When published, these will be designated as the Hay collection and Lewis collection respectively to indicate their provenance; we would welcome the loan of other pictures.

The first of these pictures dates back to 1918 and shows Lewis setting up his camera for bird photography at the Colchester Military Hospital, where studies on the effort syndrome were performed (Hay collection).

DENNIS M KRIKLER

Br Heart J 1990;63:69–70

LETTERS TO THE EDITOR

When does the risk of acute coronary heart disease in ex-smokers fall to that in non-smokers?

SIR,—The paper by Dr Robinson and his colleagues (1989;62:16–9) used such completely inappropriate methods that its conclusions should not be accepted. First, it notes that, among patients with acute myocardial infarction or unstable angina, those who smoked were a lot younger than those who did not (and had slightly lower serum concentrations of cholesterol and blood pressure). Next it notes that if smokers give up smoking, then after several years their other risk factors will, in aggregate, tend to get worse (one important reason for this being, of course, that the ex-smokers will inevitably get progressively older), until the ex-smokers' overall risk score resembles that of non-smokers. Finally—and this is what is completely inappropriate—Robinson *et al* infer from these two observations that it takes several years after stopping smoking for the risk of myocardial infarction among ex-smokers to fall to that among non-smokers.

Not only is the cited evidence irrelevant to this conclusion, but also the conclusion itself is wrong. Several large and epidemiologically appropriate studies of the effects of smoking cessation have already been done, and have indicated substantial benefit within a short time of stopping smoking.

RICHARD PETO
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This letter was shown to the authors, who reply as follows:

SIR,—Dr Peto's difficulties with our interpretation of both our data and previously published research were ones that we discussed in our paper. Our paper rested on this assumption: that people who get heart attacks have, roughly speaking, all reached the same point in the development of their coronary disease. Smokers, because they smoke, have lower levels of other risk factors. If ex-smokers have a rapidly declining risk after stopping we would expect to see only those ex-smokers whose heart attack came shortly after giving up smoking to present with risk factor levels typical of smokers. The other ex-smokers would have risk factor levels similar to those who never smoked. Our paper examined data on patients after a first episode of myocardial infarction or unstable angina to see if this was so. Dr Peto's criticism would be valid if we had examined a group of people in the general population, but what he does not take into account is that we assumed that all the patients in our study had equivalent progression of coronary disease. If one rejects this assumption one must of course follow Dr Peto in rejecting our conclusions, but it is an assumption that we believe to be tenable, if simplistic, over large numbers of patients with coronary disease. We did not note that "if smokers give up smoking, then after several years their other risk factors will tend to get worse". This conclusion could not, furthermore, be drawn from the data we presented and we believe the reverse to be true.

Nor is the published evidence on smoking cessation as clear cut as Dr Peto suggests: What are "substantial benefits" and what is "within a short time of stopping"? As we point out, some studies showing absence of added risk in ex-smokers were too small to detect the sort of risk we would expect, and although some large epidemiological studies have indeed shown substantial benefit, others, notably the report of Cook and his colleagues from the British Regional Heart Study,[1] have not

It would be nice to think that a chronic insult to the cardiovascular system such as smoking, which leaves a permanent legacy in other physiological systems, leaves behind no lasting change in the risk of heart attack, but from the present state of the evidence this is unproven. To treat it as proven, furthermore, would lead us to regard smoking in younger people as cardiovascularly safe, because they can give up before they reach the age at which they might have a heart attack. The question of a lasting residual risk from smoking is therefore an important one—too important, we believe, to regard as being answered by published studies.

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KILLIAN ROBINSON
RISTEARD MULCAHY
Cardiac Department,
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1 Cook DG, Shaper AG, Pocock SJ, Kussick SJ. Giving up smoking and the risk of heart attacks a report from the British Regional Heart Study. *Lancet* 1986;ii:1376–80.

Fatal intrathoracic haemorrhage after cardiopulmonary resuscitation and treatment with streptokinase and heparin

SIR,—Haugeberg *et al* (1989;62:157–8) reported the death of a man who was treated with streptokinase after resuscitation by cardiac massage and electrical defibrillation after presumed early myocardial infarction. Previous cardiac massage is a well-known contraindication to treatment with thrombolysis and so his death from massive intrathoracic haemorrhage is no surprise.

My question has to do with the necropsy findings. We are not told whether there was a fresh thrombotic occlusion or any evidence of an acute event in a coronary artery or its muscular territory. The patient had ST segment elevation on the electrocardiogram but no Q waves. The massive enzyme release was to be expected after massage and defibrillation and massage itself may cause posterobasal infarction through mechanical trauma to the limp empty heart.

Had this patient who died from haemorrhage after resuscitation and streptokinase had a coronary artery occlusion? I was surprised that the necropsy report made no mention of the coronary arteries.

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This letter was shown to Dr Haugeberg, who replies as follows:

SIR,—Examination of the coronary arteries showed that the left anterior descending and right coronary arteries had several atheromatous plaques but no significant stenoses. The left circumflex artery had a narrow lumen with a stenotic area 3 cm distal to its origin. In this area there was intimal discoloration compatible with the presence of a lysed thrombus. There were several other atheromatous plaques distal to this stenosis but no signs of other thrombi.

The myocardium showed signs of recent transmural infarction affecting the posterior wall of the left ventricle, including the posteromedial papillary muscle.

These findings support the diagnosis of posterior myocardial infarction secondary to a thrombotic occlusion of the left circumflex coronary artery.

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Norway

BOOK REVIEW

Heart Disease in Women. Ed Pamela S Douglas. (pp 316; £50) (Vol 19/3 of Cardiovascular Clinics. Ed AN Brest). Philadelphia: FA Davis Company, 1989. ISBN 0-8036-2751-3

On first thought there does not seem to be a need for a book on heart disease in women, because the effects on the heart and circulation of the most important difference between men and women are well covered by chapters on pregnancy in standard cardiological texts—a good example being that by Perloff in Braunwald's *Heart Disease*. There is also Szekely and Snaith's *Heart Disease and Pregnancy*, a classic monograph based on three decades' of clinical experience

First thoughts on this new volume are vindicated by the second chapter, on the cardiovascular response to exercise, which concludes after 18 fact-filled pages that the overall response of the cardiovascular system to exercise is similar in men and women. However well written, accounts of conditions that have similar manifestations in either sex are gratuitous in such a book, and could equally well appear under the title "Heart Disease in Men".

In the section on pregnancy and heart disease, Oakley advises against the use of tissue valves in women planning a family, and states that there is no justification for using heparin rather than warfarin during the first part of pregnancy. In a later chapter on therapeutics and management during pregnancy, contrary opinions are offered by Rutherford and Hands. One would have to look elsewhere, perhaps to *Textbook of Medical Treatment* edited by Girdwood and Petrie, for a full and balanced account of reproductive prescribing. There are duplicated accounts of the physiological changes of pregnancy and there are other signs of deficient editorial control, my favourite being "bibasilar rales can occasionally be heard bilaterally"

The section on coronary heart disease in women is excellent, with a breadth of view that is lacking from the symposium proceedings *Coronary Disease in Young Women* edited by Oliver. Information on epidemiology, risk factors, diagnostic testing, and treatment are brought together in a scholarly review. A whole chapter by Osbakken is devoted to exercise testing in women, which poses particular problems, not entirely because the pretest probability of coronary artery disease is less than that in men. Diagnosis of coronary disease by probability analysis combining clinical findings and several test results is discussed and illustrated with a comprehensive nomogram based on the work of Patterson *et al*.

The key role of oestrogens in the protection of pre-menopausal women from coronary artery atherosclerosis, and a possible interaction with social factors, is indicated by an account of studies in macaque monkeys. Low status monkeys had depressed ovarian function and more coronary atherosclerosis than their overbearing sisters. There is a timely account of the related topic of oestrogen replacement therapy and coronary disease.

The final section of this collation is a consideration of selected diseases including systemic and pulmonary hypertension, mitral valve prolapse, rheumatic heart disease, and cardiomyopathy. The prevalence of all these conditions is different in women and men. While it may be helpful to have this set out within one set of covers it does not make for interesting reading.

Nowhere is there a mention of syndrome X.

JOHN RAWLES

NOTICES

British Cardiac Society

The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts is 19 January 1990.

Receptors of the brain, lung, and heart

A meeting entitled Receptors of the Brain, Lung and Heart: State of the Art will be held on 24 and 25 May 1991 at the Hotel Okura, Amsterdam. Further information from Cader Research BV, PO Box 85, 4854 ZH Breda/Bavel, The Netherlands.

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

General

Three complete sets of the manuscript (including 3 sets of figures) are submitted. ☐

The manuscript is typed double spaced throughout on one side only on 22 x 28 cm opaque white bond paper with 3 cm margins all around. ☐

The manuscript is arranged as follows: (1) title page, (2) abstract, (3) text, (4) references, (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1. ☐

The last name of the first author is typed at the top right corner of each page. ☐

A covering letter is signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. ☐

Title page

The title and authors' names are typed on the title page. ☐

Case reports may have only three authors. ☐

The address(es) of the institutions from which the work originated with the authors' names are listed underneath. (If there is more than one address several authors' names can be grouped under each appropriate address; strict order of authors' names is not necessary here.) ☐

The full name, exact *postal* address with postal code, and telephone number of the author to whom communications, proofs, and requests for reprints should be sent are typed at the bottom. ☐

Abstract

An abstract is typed double spaced on a separate page. ☐

The abstract is substantive rather than purely descriptive. ☐

Abbreviations other than standard SI units of measurement are not used. ☐

Text

Measurements are given in SI units. ☐

Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction). ☐

Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984; **51:** 1–6). ☐

Appropriate headings and subheadings are provided. ☐

Every reference, figure, and table is cited in the text in numerical order. (Order of mention in text determines the number given to each.) ☐

Acknowledgments and details of support in the form of grants, equipment, or drugs are typed at the end of the text, before references. ☐

References

References are identified in the text by arabic numerals; no more than three references are cited for any one statement. ☐

References are typed double spaced on sheets separate from the text (*numbered consecutively in the order in which they are mentioned in the text*) in the Vancouver style. ☐

Journal references contain *inclusive* page numbers; book references contain *specific* page numbers. ☐

Citations of abstracts and letters should be indicated in parentheses. ☐

Personal communications, manuscripts in preparation, and other unpublished data are not cited in the reference list but are mentioned in the text in parentheses. ☐

Abbreviations of journals conform to those used in *Index Medicus*, US National Library of Medicine. The style and punctuation of the references follow the format illustrated in the following examples:

Journal: (list *all* authors if six or less; otherwise list first three and add *et al*; do not use full stops after authors' initials)

31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984; **52:** 304–8.

Chapter in book:

28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1968: 134–9.

Book (personal author or authors): (all book references should have specific page numbers)

36 Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea and Febiger, 1981: 549–63.

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Figure legends are typed double spaced on sheets separate from the text, and figure numbers correspond with the order in which figures are presented in the text. ☐

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Three sets of unmounted glossy prints (not originals) of each photograph and drawing are submitted in three separate envelopes. ☐

Figures, particularly half tones and ECG tracings, have been submitted with the following guidelines in mind: the detail on the figure is sufficiently clear to withstand reduction and special features are designated by arrows. ☐

Black ink is used for all line drawings. Decimals, lines, etc *must* be strong enough for reproduction. ☐

The first author's last name, figure number, and "top" are indicated on the back of each illustration in light black pencil, preferably on a gummed label. ☐

Figure title and caption material appear in the legend not on the figure. ☐

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Br Heart J 1990;63:73

BRITISH
HEART
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Editorial

Should coronary angiography be performed in district hospitals?

Arrangements for the optimal distribution and delivery of specialist cardiological care are haphazard to the point of being kaleidoscopic. Changes both in the type of cardiac disorders requiring specialist assessment and also in technological advances—most strikingly in echocardiography and exercise testing—have effectively devolved triage to district general hospitals.[1] With increasing indications for intervention the question whether coronary angiography should be provided by distict hospitals will undoubtedly have to be answered in the next decade.

Questions about the provision of facilities are invariably complex because they encompass geographical, financial, clinical, professional, and political considerations. In such complex discussions, facts are often conspicuous by their absence. The article from St George's Hospital in the current issue (page 74), however, describes the current risks of coronary angiography and the extent to which immediate access to cardiac surgery can reduce mortality associated with the unavoidable complications of the investigation.[2]

The results show that case selection rather than the seniority of the operator was a major determinant of complications. Also the brachial approach was associated with a higher incidence of dissection of the main stem of the left coronary artery. This may be because the brachial approach is usually chosen for patients with clinically overt peripheral vascular disease, who are more likely to have severe coronary disease. The pre-shaped coronary artery catheters that were used from the arm may also have contributed to this association with dissection. Since the St George's study 6 French gauge catheters have become more generally used and this refinement may have reduced the incidence of dissection of the main stem of the left coronary artery.

Dr Stewart and his colleagues have confirmed that potentially fatal problems can still arise after coronary angiography and that emergency surgery is important in ameliorating the long term effect of these risks. There can be little doubt that to be effective surgery must be performed as soon as possible, with 4 hours being the limit for successful revascularisation.[3] Against this, we have to offset the likelihood of an increase in mortality if patients have to join a waiting list at major regional centres rather than being investigated more quickly in a district hospital. Would locally based diagnostic coronary angiography hasten life saving surgical intervention for left main stem or three vessel coronary artery disease in patients without either unstable symptoms or severely impaired left ventricular function? The St George's study quantifies one side of the equation—that is, the risks of investigation without surgical cover. Now the other side deserves attention.

There is a third question associated with the provision of coronary angiography in district hospitals. If patients are to face an inevitably increased risk, albeit small in absolute terms, will the quality of images from the procedure in the district hospital without surgical cover justify this risk by improving and expediting management decisions? We recently looked at image quality on standard video tape recordings with an image intensifier at Newham General Hospital.[4] Vessel patency after thrombolysis was accurately assessed by the district hospital video images. The sensitivity for important disease in the circumflex artery was only 40% when the video images were compared with regional centre live film. This would inevitably have led to incorrect management decisions being made because of the inferior image quality. The cardiac surgeon who also assessed the video tapes reached a similar conclusion.

The group from St George's Hospital has shown that any trend towards devolution of diagnostic coronary angiography away from the protective environment of on-site cardiac surgical cover will add a risk to the procedure. Such a change in the provision of resources should be considered only if appropriate capital investment is made to ensure that the diagnostic value of the resultant angiogram is sufficiently high to enable sound clinical decisions to be made and if it can be shown that the improved access to angiography is likely to reduce waiting list mortality.

PETER MILLS

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1 Ross J, Gilpin E, Madsen E, *et al.* A decision scheme for coronary angiography after acute myocardial infarction *Circulation* 1989;79: 292–303.
2 Stewart JT, Gray HH, Ward DE, Pumphrey CW, Redwood DR, Parker DJ. Major complications of coronary arteriography: the place of cardiac surgery. *Br Heart J* 1990;63·74–7.
3 Spencer FC. A critique of emergency and urgent operations for complications of coronary artery disease. *Circulation* 1989;79(suppl I):160–2.
4 Ranjadayalan K, Mills P, Sprigings D, Mourard K, Magee P, Timmis A. Coronary arteriography in the radiology department of a district general hospital: feasibility, safety, and diagnostic accuracy *Br Med J* 1990;300: (in the press).

Br Heart J 1990;63:74–7

ORIGINAL ARTICLES

Major complications of coronary arteriography: the place of cardiac surgery

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Abstract

The records of the catheter laboratory at St George's Hospital between 1983–1988 were reviewed to determine how often emergency coronary bypass surgery was performed because of a complication arising during elective coronary arteriography. A total of 11 216 cardiac procedures were performed; 5781 were confined to left ventricular angiography and coronary arteriography in patients with suspected coronary artery disease. Fourteen patients, whose investigation had been considered routine, suffered profound circulatory collapse during the procedure. Emergency cardiac surgery was undertaken in 13, with long term survival in 10.

This experience suggests that, even in patients considered to be at low risk, there were major complications requiring emergency coronary surgery in at least 2·4 per 1000 coronary arteriograms performed. Survival after emergency cardiac surgery in these patients was 77%. These findings and the access to cardiac surgery should be considered when the development of facilities for cardiac catheterisation is planned.

In Britain facilities for cardiac catheterisation have developed alongside those of cardiac surgery, usually within the same hospital. In recent years, however, the demand for cardiological services, both invasive and non-invasive, has expanded and it has been suggested that there should be greater responsibility for investigation and treatment in the district general hospitals. Under such a system, district cardiologists, many of whom are trained in invasive techniques, would be responsible for certain procedures that have traditionally been performed in the referral centres, such as permanent pacemaker implantation, and "low risk" diagnostic cardiac catheterisation.

Underlying this policy is the assumption that the risks of catheterisation without surgical back up at the same site would be negligible, because those patients who were clearly at high risk from the procedure, such as patients with unstable symptoms or pulmonary oedema, would still be studied at the referral centres. While it is true that most high risk patients can be identified readily, several major complications of cardiac catheterisation, for which emergency cardiac surgery may be indicated, are unpredictable.

Method

We reviewed the records of our cardiac catheter laboratory to determine the frequency of unexpected major complications leading to emergency cardiac surgery. We restricted our review to patients being investigated because of chest pain (with left ventriculography and coronary arteriography) in an attempt to establish the probable minimum risk.

Results

The records of the cardiac catheter laboratory at St George's Hospital, London for the years 1983–1988 were reviewed. In the 6 years studied, 11 216 cardiac procedures were performed. Left ventricular angiography and coronary arteriography in patients with suspected coronary artery disease was the sole investigation in 5781 cases (79% men, 21% women). The remaining 5435 patients underwent pacing procedures, electrophysiological studies, pericardial tap, percutaneous coronary angioplasty, endomyocardial biopsy, or were investigated for the assessment of valve disease (including percutaneous balloon dilatation of valves), or after previous coronary artery bypass surgery. Patients who were clearly at a higher risk from coronary arteriography, such as those with post-infarction ventricular septal defects (n = 31), were also excluded from this analysis. Included in the 5781, however, is an unknown number of patients who were studied as emergencies because of unstable angina, but who had no catheter-related complication.

Eighteen (0·3%) of the 5781 patients were referred for urgent operation because of acute coronary dissection (n = 6), acute coronary occlusion (n = 7), severe global ischaemia (defined as persistent electrocardiographic change, chest pain, and hypotension after contrast injection into the coronaries (n = 3), or deterioration of pulmonary oedema (n = 2, left ventriculography not performed). In each case the decision to request urgent surgical assistance was made by a consultant cardiologist.

Retrospective review of the case notes showed that four patients (three men, one

Nature of complications of arteriography and outcome after emergency operation

Patient	*Route*	*CAD*	*Complication*	*Outcome*	*Postoperative ECG*
1	Femoral	2VD (LAD and Cx)	Occluded LMS. Hypotension	Sternal abscess	Generalised T wave flattening
2	Brachial	?	Dissection LMS. Hypotension, ECM	Symptom free	Loss of R wave voltage in anterior leads
3	Femoral	?	Occluded LMS.	Symptom free	Loss of R wave voltage in anterior leads
4	Femoral	SVD (LAD)	Dissection LMS Hypotension, ECM	Reduced effort tolerance Impaired LV function	Anterior Q waves
5	Brachial	3VD	Asystole, and hypotension with RCA injection Paced	Symptom free	No change
6	Brachial	SVD (LAD)	Cx dissection. Anterior ST segment elevation. Pain, hypotension	Symptom free	Anterior Q waves
7	Brachial	2VD (LAD and OM)	RCA dissection Inferior ST segment elevation	Symptom free	No change
8	Femoral	3VD with LMS stenosis	Hypotension and bradycardia	Symptom free	No change
9	Femoral	2VD (LAD and RCA)	Occluded LAD. Anterior ST segment elevation. Hypotension	No cardiac symptoms Pedal gangrene	Anterior Q waves
10	Brachial	3VD	Cx occlusion. Pain Hypotension Widespread ST segment depression	Symptom free	Loss of R wave voltage in anterior leads
11	Brachial	3VD	Hypotension and VF after LV angiogram. ECM	Died on bypass	
12	Brachial	3VD with LMS stenosis	LMS dissection Hypotension. ECM. Widespread ST segment elevation	Died 2 days postop. Persistent low output state	Anterior Q waves RBBB
13	Brachial	?	LMS dissection. Hypotension, asystole	Died 6 weeks postop Below knee amputation, low output state	Anterior Q waves

LMS, left main stem coronary artery, LAD, left anterior descending coronary artery, Cx, circumflex coronary artery, RCA, right coronary artery, OM, obtuse marginal branch of circumflex coronary artery, ECM, external cardiac massage, LV, left ventricular, VF, ventricular fibrillation; RBBB, right bundle branch block, SVD, single vessel disease, 2VD and 3VD, two and three vessel coronary artery disease

woman; age 56–74, mean 64 years) had clearly been at high risk before the procedure. All had continuing chest pain despite maximal medical treatment, and three had pulmonary oedema at the time of catheterisation. All underwent emergency coronary artery bypass surgery, but none survived to leave hospital. These high risk patients are excluded from further analysis.

In the remaining fourteen patients (0·24% of the total) who were referred for urgent surgery (eight men, six women; age 43–70, mean 59 years) the investigation had been considered routine and eight were day case procedures. Acute coronary dissection occurred in six (43%), acute coronary occlusion in five (36%), and global ischaemia in three (21%).

There was multivessel coronary artery disease in eight (57%) patients, but significant left main coronary artery stenosis was seen in only two patients. There was obstruction of the left main coronary artery (from either dissection or occlusion without dissection) in six (43%): in three the proximal coronary anatomy remains unknown, one had severe triple vessel disease without significant left main disease, and in the other two there was relatively minor disease (table).

In five (36%) patients the exact coronary anatomy had not been established at the time of collapse; one had a cardiac arrest after the left ventriculogram and could not be resuscitated, and in the other four there was occlusion or dissection (with persistence of contrast) of the left main coronary artery after the initial left coronary injection. Postmortem study of two of these five patients showed triple vessel coronary disease (including left main stem disease in the patient who collapsed after ventriculography alone).

Twelve patients (86%) went immediately in the operating theatre for emergency coronary artery bypass surgery, one patient (7%) died in the catheter laboratory before transfer to theatre was possible, and one patient (7%) underwent operation 2 hours after cardiac catheterisation. Seven (58%) of the 12 who had immediate operations required full resuscitation procedures, including external cardiac massage, during transit from the catheter laboratory to the operating theatre; the other five (42%) remained appreciably hypotensive, but with a stable rhythm and cardiac output until the start of cardiopulmonary bypass.

After emergency operation three (23%) patients died in hospital and the 10 (77%) who survived were alive at long term follow up. The three postoperative deaths occurred in the group of patients who had required cardiac massage until the establishment of cardiopulmonary bypass.

The catheter operator was a consultant cardiologist in seven (50%) cases, a senior registrar in three (21%) cases, and a registrar in four (29%) cases. To put these figures in perspective, 45% of all procedures are performed by three consultant cardiologists, 20% by the senior registrar, and 35% by registrars. The femoral approach was used in six (43%) of the 14 patients, while the brachial approach (using a preformed brachial catheter) was used in the remaining eight (57%) patients. Overall, 70% of elective coronary arteriograms are performed via the femoral artery and 30% via the brachial artery at St George's Hospital.

There were postoperative complications in three (30%) of the 10 survivors. One patient who had required support with an intra-aortic balloon pump while cardiopulmonary bypass was stopped, later had peripheral gangrene, but did not require further operation. She had not experienced any cardiac symptoms when seen postoperatively in outpatients, but she died suddenly 2 years after operation. This was the only late death. One man experienced episodes of infection of the sternal wound, which required operative debridement, and the third had clearly suffered an extensive anterior myocardial infarct resulting in left ventricular dysfunction. When seen in outpatients he had reduced effort tolerance, although his symptoms were stable on treatment with a diuretic and an angiotensin converting enzyme inhibitor. The remaining nine patients (90%) were free of cardiac symptoms when reviewed in the outpatient clinic, although in six (60%) there were changes in the postoperative electrocardiogram consistent with infarction (table).

Discussion

The risks of cardiac catheterisation and angiography are well recognised. These are usually divided into minor problems such as transient chest pain or arrhythmia and major complications such as arterial injury and embolisation, stroke, myocardial infarction, and death. There has been debate over the relative safety of the brachial and femoral routes for cardiac catheterisation.[1-3] The data presented here seem to suggest that there is a greater risk of major complication when the brachial approach is used. However, in this retrospective survey we made no attempt to match the groups and they may not be directly comparable. It is our usual policy to catheterise day patients from the arm, but patients with generalised arterial disease, which includes iliofemoral disease, are more likely to be studied from the brachial route. Such patients are more likely to have severe multivessel coronary disease and may be at higher risk irrespective of the approach used.[2 4]

In 1972, the ad hoc Committee on Coronary Artery Surgery of the Inter-Society Commission for Heart Disease Resources recommended that deaths associated with coronary arteriography, in the United States of America, should not exceed 0·3%.[5] In 1974, Judkins and Gander suggested that a mortality rate in excess of 0·1% was unacceptable,[1] but later reports have shown that, when all cases are considered, most laboratories have a mortality of 0·1–0·2%.[4 6 7] It is clear, however, that the risk to the patient is closely related to his functional class and the severity of coronary artery disease. Left main stem disease is said to increase the risk of death by 6·8 times, and factors such as unstable angina, congestive heart failure, multiple ventricular extrasystoles, and hypertension also increase the risk.[2] Triple vessel disease and age greater than 60 years have also been associated with increased mortality in one report.[4]

Conversely, it has been suggested that in low risk patients (functional class I and II of the New York Heart Association classification) mortality may be as low as 0·02%.[7] In a paper presented recently to the British Cardiac Society, it was suggested that invasive cardiac investigations, and even coronary angioplasty, could be performed safely in the absence of on site cardiac surgery.[8] The numbers in this study were very small, however (273 diagnostic coronary arteriograms and six coronary angioplasties), and as a result its conclusions must be interpreted with caution. The delay before emergency operation could be undertaken at another hospital, in the two patients in whom it was required, was 3 hours. A recent paper reporting the results of cardiac catheterisation as a day case procedure is relevant to this issue[9] Oldroyd *et al* reviewed 900 patients selected for day case catheterisation, and therefore, by definition, considered to be at low risk from the procedure (56% had one or two vessel disease). Forty patients (4·4%) could not be discharged the same day because of some complication of the procedure or because urgent, but not immediate, coronary artery surgery was considered necessary. For the group as a whole the incidence of death was 0·2%, non-fatal myocardial infarction 0·7%, and major vascular injury 0·2%. Mortality was 0·3% in the subgroup that underwent coronary angiography and left ventriculography alone. It was not stated how many patients underwent immediate operation from this series.

Our findings accord with those of Oldroyd *et al.* We believe that without the benefit of emergency cardiac surgery at least 10 of our 14 "low risk" patients would have died. Thus while mortality for elective left ventriculography and coronary arteriography was $<0·1\%$ in our series, it would almost certainly have been $\geqslant 0·2\%$ had we not had recourse to emergency surgery. It is of course impossible to prove that the patients referred for emergency operation benefited from its availability, but the severity of haemodynamic disturbance seen makes it very likely that they would have died without operation. Furthermore, despite the experience of Bayliss *et al*, we believe that there would not have been time to transfer these patients elsewhere for operation.

Survival after emergency operation in this group of patients was 77% and in most left ventricular function, judged by symptomatic criteria, was adequate. That there were no survivors in patients identified as being at high risk suggests that heroic attempts to resuscitate such patients may be inappropriate.

By restricting our survey to the simplest type of left heart investigation, which is likely to form the greatest part of the workload of any cardiac catheter laboratory, we believe that we have shown the minimum risk of major unexpected complications. If patients with unstable symptoms, heart failure, complex congenital disease, or valve disease were included the risk is likely to be higher. Unfortunately, we cannot tell from this retrospective review of the catheter laboratory records how many other patients who would have been considered high risk because of unstable symptoms had uneventful coronary arteriography. By reducing the size of the denominator, the exclusion of such patients would have resulted in an even higher calculated risk.

Our experience suggests that the mortality associated with cardiac catheterisation in patients perceived to be at low risk is likely to be greater than two patients in every 1000. This may be reduced by having surgical facilities immediately available. These findings should be borne in mind when the development of new cardiac catheterisation facilities is considered; it may be more desirable to expand the existing facilities at the regional centres and to encourage their use by appropriately trained cardiologists from district hospitals.

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VIEWS FROM THE PAST *Sir Henry Dale*

Immediately after qualifying in medicine Dale joined E H Starling in the physiology department at University College, London, and then spent 10 years at the newly established Wellcome Laboratories, where he became director. His early interest in the properties of ergot led him to study adrenaline, histamine, and acetylcholine at the National Institute of Medical Research, where he also became director. For his work on the chemical transmission of nerve impulses he shared the Nobel Prize in physiology or medicine with his friend Otto Loewi in 1936 (Lewis Collection).

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High density lipoprotein cholesterol and triglycerides as markers of angiographically assessed coronary artery disease

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Abstract

Serum triglycerides, high density lipoprotein (HDL) cholesterol, and total cholesterol were measured in 698 patients examined by angiography. The ratio of HDL cholesterol to total cholesterol was significantly lower in patients with single, double, and triple vessel disease than in patients without disease. The serum concentration of triglyceride was significantly higher in patients with single, double, and triple vessel disease than in those without coronary artery disease. Similar proportion of patients with coronary artery disease and without had serum cholesterol concentrations of ≥6·5 mmol/l, but total cholesterol was significantly higher in patients with single, double, and triple vessel disease than in those without. HDL cholesterol (<1·0 mmol/l), triglycerides (>2·0 mmol/l), and the ratio of HDL cholesterol to total cholesterol (<0·20) were significantly better than total cholesterol as indicators of coronary risk.

Since 1959, when Albrink and Man suggested that raised concentrations of serum triglyceride might be related to the pathogenesis of ischaemic heart disease,[1] several investigators have measured lipids in healthy individuals and those with this disease.[2-4] Clinical studies have established that a raised serum concentration of total cholesterol is an aetiological factor in coronary artery disease.[5 6] Fewer data are available on the possible value of raised concentrations of triglyceride in predicting the occurrence of the disease in apparently healthy men. In a follow up prospective study in Sweden the occurrence of new events of ischaemic heart disease was related to serum triglycerides and cholesterol, which were risk factors for coronary artery disease that were independent of each other. The highest risk of coronary artery disease was associated with a combined increase of those two serum lipids.[7] Follow up studies from other areas in Sweden confirmed that serum triglycerides were a risk factor for ischaemic heart disease.[8 9] There are more recent both primary and secondary prevention studies, in which a beneficial effect was closely related to a reduction of serum triglycerides rather than to the reduction in serum cholesterol.[10 11] The serum concentration of total cholesterol in Finland is exceptionally high (mean 6·3 mmol/l) even in healthy people and the relative importance of lipid components is not necessarily similar to that in other countries.

The aim of this study was to determine whether total cholesterol, high density lipid (HDL) cholesterol, and triglycerides are discriminators of coronary artery disease. In addition, we attempted to find out whether lipid concentrations are related to the extent of disease.

Patients and methods

We studied 698 patients aged 29–69 years admitted during 1985–7 to Tampere University Hospital for elective coronary angiography for the investigation of chest pain. Lesions in coronary arteries were graded visually from 0 to 4: 0 = normal, 1 = >50% stenosis in one vessel, 2 = >50% stenosis in two vessels, 3 = >50% stenosis in three vessels. Coronary angiography was performed by the Judkins technique via the right femoral artery. Twenty four hours before catheterisation serum total cholesterol, HDL cholesterol, and triglycerides were measured after a 12 hour fast. All patients were ambulant up until the day on which serum lipids were measured, at least three months after myocardial infarction. We used a cut off value of 6·5 mmol/l for total cholesterol and a cut off value of 2·00 mmol/l for triglycerides, which were the arbitrary upper limits of normal at Tampere University Hospital. For HDL cholesterol we used a cut off value of 1·0 mmol/l, which was the lower limit of normal. For the ratio of HDL cholesterol to total cholesterol we used a cut off value of 0·20, which is useful index of the risk of coronary artery disease.[12]

The patients were divided into four groups on the basis of the angiographic results: 63 patients did not have clinically important coronary artery disease (that is stenosis of <50% of the transluminal diameter in all segments), 124 patients had single vessel disease, 192 patients double vessel disease, and 319 patients triple vessel disease. Table 1 shows the smoking habits, the use of β blockers, previous myocardial infarction, and the sex ratio in the four groups.

Serum cholesterol was measured by the Monotest kit from Boehringer Mannheim with an Olli C semiautomated analyser (Kone Oy, Finland). The polyethyleneglygol precipitation method was used to measure HDL cholesterol together with the Monotest for cholesterol. Concentrations of serum triglycerides were measured by an enzymatic method (Boehringer Mannheim).

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Table 1 Percentage of smokers, use of β blockers, previous myocardial infarction, and male sex in relation to findings of coronary angiography

	No lesion (n = 63)	*Single vessel (n = 124)*	*Double vessel (n = 192)*	*Triple vessel (n = 319)*	*All*
Smokers	10**	22	29	16	20
Use of β blockers	63*	75	81	84	80
Previous myocardial infarction	22***	63	61	60	56
Male sex	62*	81	88	88	84

*$p < 0·05$, **$p < 0·01$, ***$p < 0·001$ compared with other groups.

The data from the four groups of patients were compared by an analysis of variance and when the F ratio was significant we used a Student-Newman-Keuls test. Triglyceride values were log transformed before statistical analysis but untransformed values are given in the text and tables. To analyse the frequency of patients by a χ^2 test we combined the three groups with coronary artery disease to give a group with disease and one without. A Bartlett-Box test and a multiple discriminant analysis were used to assess the lipid values as discriminators of coronary artery disease.

Results

Table 2 summarises the data on serum lipids for each group of patients, defined according to the number of coronary arteries with ≥50% stenosis. The mean values for total cholesterol were significantly ($p < 0·01$) higher in patients with single, double, and triple vessel disease than in those without disease. Serum HDL cholesterol was significantly ($p < 0·001$) higher in patients without coronary artery disease than in patients with single, double, or triple vessel disease. The ratio of HDL to total cholesterol was significantly ($p < 0·001$) lower in patients with single, double, and triple vessel disease than in patients without disease. The mean values for triglycerides were significantly ($p < 0·01$) higher in all patients with disease than in patients without.

Total cholesterol was ≥6·5 mmol/l in 20 (31·8%) patients without disease and in 273 (43·0%) patients with disease; the difference was not statistically significant (table 3). HDL cholesterol was ≤1·0 mmol/l in 28·6% of 63 patients without disease and in 52·1% of 635 patients with disease ($p < 0·001$). The best discriminators between patients without and with disease was serum triglyceride (>2·0 mmol/l) and in the ratio of HDL to total cholesterol (<0·20) ($p < 0·001$) (table 3). There was a significant inverse correlation between HDL cholesterol and serum triglycerides ($r = -0·382$, $p < 0·001$). Multiple discriminant analysis showed that the ratio of HDL to total cholesterol was a better indicator of coronary artery disease than other lipid values.

Discussion

The Study Group of the European Atherosclerosis Society recommends dietary and other measures to reduce risk in most people with serum cholesterol values of 5·2–6·5 mmol/l.[13] Lipid lowering drugs should then be considered if total cholesterol remains at 6·5 mmol/l or higher. In the present study, however, 31·8% patients without disease and 43·0% with disease had total cholesterol concentrations of ≥6·5 mmol/l. This non-significant difference between patients with and without disease was equal whatever the different cut off points of total cholesterol (for 0·1 mmol/l intervals between 6·0 and 7·0 mmol). These results show that total cholesterol measurement alone is not a good discriminator.

There are no firm recommendations on triglyceride measurement in risk assessment and treatment for raised triglycerides. Nevertheless, reanalysis of the Framingham data[14] indicated that serum triglycerides are independently predictive of coronary artery disease in patients with low serum concentrations of HDL cholesterol. Serum triglyceride concentrations are probably important in secondary prevention after myocardial infarction, because serum concentrations are higher in such patients[11] than in healthy individuals. In the Helsinki Heart Study gemfibrozil considerably reduced triglycerides (by 35%) but only modestly reduced low density lipoprotein (LDL) cholesterol (8% decrease) and increased HDL cholesterol (10% increase).[10] The effects on serum concentrations of triglycerides, low density lipoprotein cholesterol, and high density lipoprotein cholesterol contributed to a beneficial outcome.

Those treated with cholestyramine in the seven year Lipid Research Clinics study showed mean reductions in plasma concentrations of total and low density lipoprotein cholesterol of 13 and 20% respectively; an average increase of 3% in HDL cholesterol and the slight rise in triglycerides were not significant.[15] A 17% reduction in all definite end points for ischaemic heart disease was seen in the Lipid Research Clinics study and a 34% reduction in the Helsinki Heart study, in which the greatest relative change in serum lipid

Table 2 Age, serum total cholesterol, HDL cholesterol, triglycerides, and the ratio of HDL cholesterol to total cholesterol in patients without coronary artery disease and in those with single, double, or triple vessel disease

Variable	*No lesion (n = 63)*		*Single vessel (n = 124)*		*Double vessel (n = 192)*		*Triple vessel (n = 319)*		*Statistical significance in ANOVA*
Age	52·2	(0·91)	49·4	(0·74)	53·5	(0·67)	54·9	(0·33)	
Total cholesterol (mmol/l)	5·93	(0·15)	6·34	(0·12)	6·53	(0·09)	6·52	(0·06)	$p < 0·01$
HDL cholesterol (mmol/l)	1·29	(0·05)	1·13	(0·03)	1·10	(0·03)	1·07	(0·01)	$p < 0·001$
Triglycerides (mmol/l)	1·77	(0·11)	2·39	(0·13)	2·50	(0·13)	2·59	(0·11)	$p < 0·01$
HDL:Total cholesterol	0·22	(0·01)	0·18	(0·01)	0·17	(0·01)	0·17	(0·01)	$p < 0·001$

Values are given as mean (SEM). ANOVA, analysis of variance In Student-Newman-Keuls test the statistical difference was significant between the group without coronary artery disease and all other groups with coronary artery disease, but not between groups with single, double, and triple vessel disease.

Table 3 Percentage of patients in relation to serum lipid

	No lesion (n = 63) (%)	*Disease (n = 635) (%)*	χ^2	*Significance*
Total cholesterol >6·5 mmol/l	31·8	43·0	3·2	NS
HDL cholesterol <1·0 mmol/l	28·6	52·1	15·3	p < 0·001
Triglycerides >2·0 mmol/l	28·6	52·4	21·4	p < 0·001
HDL:Total cholesterol <0·20	47·6	75·1	30·2	p < 0·001

concentrations was seen in serum triglycerides; this had only a small effect on the incidence of coronary artery disease.[16] Several American studies have shown that high concentrations of serum cholesterol are a significant coronary risk factor,[5,6] but in the United States the role of triglycerides remains controversial.

The importance of HDL cholesterol concentration was shown in several large epidemiological studies.[17,18] These surveys either indicated that individuals with low concentrations of HDL cholesterol have a higher prevalence of coronary artery disease or that a low HDL cholesterol concentration is a common antecedent of clinical coronary artery disease. There is evidence that triglycerides constitute an independently predictive risk factor for ischaemic heart disease in individuals with low serum concentrations of HDL cholesterol.[14] Raised triglycerides are a risk factor for ischaemic heart disease especially in middle aged men.[19] A reduced fibrinolytic capacity was often found in patients with myocardial infarction and hypertriglyceridaemia.[20] Moreover, follow up studies showed that hypertriglyceridaemia was an independent risk factor for reinfarction, an association possibly connected with a predisposition to thrombosis through a coexisting high concentration of plasminogen inhibitor.[21] Hypertriglyceridaemia is a thrombogenic factor rather than an atherogenic factor.

The findings of this study re-emphasise the importance of hypertriglyceridaemia and reduced HDL cholesterol as risk factors of coronary artery disease. Similar observations were reported in England, where a raised concentration of serum triglycerides was the best discriminator between patients and controls.[22] In this study there was an inverse correlation between HDL cholesterol and triglycerides. This may seem to be a central issue in the pathogenesis of atherosclerosis, since both high concentrations of triglyceride-rich lipoproteins (very low density lipoprotein) and low concentrations of HDL are well recognised lipid risk factors for arterial disease. It is possible that the primary disturbance responsible for the low HDL may ultimately lie in triglyceride metabolism and HDL could be a mediator between the basic metabolic defect and the vascular lesion.[23]

Follow up studies from Sweden confirm that raised concentrations of serum triglycerides are a risk factor for coronary artery disease.[7–9] In the present study serum triglyceride was a good discriminator, better than total cholesterol, between patients with coronary artery disease and those without. Triglyceride concentrations were significantly ($p < 0{\cdot}01$) higher in those with single, double, and triple vessel disease than in those without disease. A raised triglyceride concentration was a significant discriminator especially in one vessel disease, when patients tended to be young or middle aged, and their total cholesterol did not differ significantly from patients without disease. Patients without disease were significantly less likely to be smokers, to be taking β blockers, and to be men than in the other groups (table 2). Smoking and selective β_1 blockers do not influence serum total cholesterol, but can slightly increase triglycerides and reduce HDL cholesterol. The smaller proportion of men among those with normal findings on coronary angiography could contribute to the higher values of HDL cholesterol. Myocardial infarction and sudden unstable angina pectoris without earlier chest pain were more commonly found in those with one vessel disease than in those with double or triple vessel disease. Also HDL cholesterol alone was a better discriminator than total cholesterol. The best discriminator in this study was a low ratio of HDL cholesterol to total cholesterol.

Total cholesterol does not discriminate between healthy people and patients with coronary artery disease. Before patients with hypercholesterolaemia (>6·5 mmol/l) are treated HDL cholesterol should be measured. The results of the present study suggest that the ratio of HDL cholesterol to total cholesterol was a better indicator of coronary risk than HDL cholesterol alone, total cholesterol, or triglycerides. Serum triglycerides give a wider discrimination than serum total cholesterol in identifying not only patients with multivessel disease but also those with important single vessel disease.

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Inflammatory response, neutrophil activation, and free radical production after acute myocardial infarction: effect of thrombolytic treatment

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Abstract

Activated neutrophils releasing proteolytic enzymes and oxygen free radicals have been implicated in extending myocardial injury after myocardial infarction. Neutrophil elastase was used as a marker of neutrophil activation and the non-peroxide diene conjugate of linoleic acid was used as an indicator of free radical activity in 32 patients after acute myocardial infarction; 17 were treated by intravenous thrombolysis. Patients with acute myocardial infarction had higher plasma concentrations of neutrophil elastase and the non-peroxide diene conjugated isomer of linoleic acid than normal volunteers or patients with stable ischaemic heart disease. Patients treated by thrombolysis had an early peak of neutrophil elastase at eight hours while those who had not been treated by thrombolysis showed a later peak 40 hours after infarction. The plasma concentration of non-peroxide conjugated diene of linoleic acid was highest 16 hours after the infarction irrespective of treatment by thrombolysis. Quantitative imaging with single photon emission tomography showed decreased uptake of indium-111 labelled neutrophils in the infarcted myocardium (as judged from technetium-99m pyrophosphate) in those who had received thrombolysis, suggesting a decreased inflammatory response.

The results indicate increased neutrophil activation and free radical production after myocardial infarction; they also suggest that thrombolysis does not amplify the inflammatory response and may indeed suppress it.

Activation of neutrophils with release of lysosomal enzymes and production of oxygen free radicals is an important part of the host defence mechanism against microbial infection. Activated neutrophils, however, have been implicated in the pathogenesis of several disease processes including emphysema, adult respiratory distress syndrome, and myocardial infarction.[1] It has been suggested that the neutrophil may cause secondary heterolytic damage of myocytes, because neutrophil depletion limited infarct size in animal models of infarction[2,3]; the damage was attributed to the release of lysosomal enzymes[4] or free radical production.[5] Further experimental evidence suggests that reperfusion of ischaemic myocardium, for example after thrombolytic treatment, may be a double edged sword with the benefits of reoxygenation being partly offset by the potential harmful effects of reperfusion injury.[6] Postulated mechanisms of reperfusion injury include plugging of small capillaries,[7] generation of oxygen free radicals,[8] calcium influx[9] and neutrophil activation with release of lysosomal enzymes.[10] Thus the neutrophil may have a role in reperfusion injury but its importance in patients has not been determined, though the clinical benefits of thrombolytic treatment are now established.[11,12]

Degranulation of neutrophils releases neutrophil elastase, a lysosomal enzyme; this has been used as a specific marker of neutrophil activation.[13] Activated neutrophils are one potential source of oxygen free radical production.[14] It is difficult to measure these unstable oxygen species but once they are generated they will react and oxidise adjacent molecules, particularly polyunsaturated fatty acids.[15] The diene conjugated non-peroxide isomer of linoleic acid (phospholipid 9, 11-linoleic acid; PL-9, 11-LA′) has been used as a marker of human free radical activity.[16] To determine if and when neutrophil activation takes place after myocardial infarction, we measured serial changes in plasma neutrophil elastase and PL-9, 11-LA′. We also investigated how these indices were influenced by reperfusion by studying patients treated with and without thrombolytic agents. Finally, because the acute inflammatory infiltrate within myocardium after myocardial infarction can be imaged,[17] we examined the effect of treatment with and without thrombolysis on the myocardial uptake of indium-111 labelled neutrophils.

Patients and methods

VALUES IN HEALTHY VOLUNTEERS AND PATIENTS WITH CHRONIC ISCHAEMIC HEART DISEASE

To establish a normal range for plasma concentrations of neutrophil elastase and the conjugated diene of linoleic acid, blood samples were taken from 35 healthy volunteers from laboratory and hospital staff. As a further control group we also studied 30 patients with a documented history of ischaemic heart disease based on coronary angiography (n = 12) or distant myocardial infarction (n = 18) (table 1).

PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Observations were based on 32 patients who

Table 1 Characteristics of healthy volunteers, patients with chronic ischaemic heart disease, and patients with myocardial infarction

			Myocardial infarction	
	Volunteers (n = 35)	*IHD (n = 30)*	*No thrombolysis (n = 15)*	*Thrombolysis (n = 17)*
Age (yr)	34 (22–63)	59 (37–76)	58 (38–74)	56 (30–69)
M/F	30.5	24 6	10.5	13 4
WBC ($\times 10^9$/l)	5 8 (3 4–9 3)	6 7 (5 2–12 6)	13 2 (9 6–23 0)	16 8 (7 9–33 7)
LVEF (%)	—	41 (18–63)	32 (15–71)	40 (24–68)
Peak creatine kinase (U/l)	—	—	1635 (522–6255)	2059 (533–6955)
Heparin (subcutaneously)	—	—	15	—
Heparin (intravenously)	—	—	—	17
Streptokinase/anistreplase	—	—	—	9/8
Lignocaine	—	—	3	5
Hydrocortisone	—	—	—	9
β Blockers	—	24	2	5
Diuretics	—	4	6	5
Deaths	—	—	2	1

WBC, white blood cells; LVEF, left ventricular ejection fraction

had sustained a recent acute anterior myocardial infarction. The diagnosis was based on the history of prolonged ischaemic chest pain, characteristic electrocardiographic changes, and increase in the enzyme creatine kinase. The patients were subdivided into the 17 who had been given intravenous thrombolysis with either 1 200 000 units streptokinase (Kabivitrum, Middlesex, UK), or 30 units of anistreplase (anisoylated plasminogen streptokinase complex (Eminase, Beecham Pharmaceuticals, Epsom, UK). The other 15 were deemed ineligible to receive thrombolytic treatment because of late admission (> 4 hours after the onset of symptoms), a history of active peptic ulceration, other source of haemorrhage, or recent cerebrovascular accident and were treated in conventional fashion. Table 1 shows the details of the two groups including drug treatment. All study times were taken from the onset of symptoms. All patients gave informed consent and the study was approved by the institute's ethics committee.

PROTOCOL

In patients with acute myocardial infarction blood was taken for full blood count and measurement of creatine kinase, neutrophil elastase, and linoleic acid (PL-9, 12-LA) and its diene conjugated non-peroxide isomer (PL-9, 11-LA′) esterified as phospholipids. Samples were taken at 6–8 hours after the onset of symptoms and every 8 hours thereafter until 48 hours. Samples were centrifuged and plasma separated immediately and held at −20°C until analysis was performed.

PL-9, 11-LA′ AND PL-9, 12-LA

The molar concentrations of PL-9, 11-LA′ and PL-9, 12-LA in plasma were measured by high performance liquid chromatography in plasma after enzymatic hydrolysis with phospholipase A_2 and solid phase sample preparation as described by Iversen *et al.*[16] The intra-assay coefficient of variation was <3·5%. The results are expressed as μmol/l.

PLASMA NEUTROPHIL ELASTASE

Human neutrophil elastase was measured by specific radioimmunoassay with rabbit polyclonal antiserum.[13] The antigen was purified from human neutrophils after leucopheresis. The antibody was specific for neutrophil elastase and measured free enzyme and enzyme complexed to the natural inhibitors α_1-proteinase inhibitor and α_2-macroglobulin equally well. The results are expressed as ng/ml and the intra-assay coefficient of variation was <5%.

IMAGING

Our previous work has shown that labelled neutrophil uptake within the myocardium can be imaged reliably providing the time from onset of infarction to reinjection of labelled cells is <18 hours.[17] Only 21 of the patients could be studied by this technique within the appropriate time limits because of limited availability of the radionuclide indium-111. The patients received 20–30 MBq of indium-111 labelled autologous neutrophils within 18 hours of the onset of symptoms. Single photon emission tomography was undertaken 24 hours after the injection of the labelled cells with an IGE 400 AT maxicamera linked to a Siemens Microdelta computer. On the following day the patients were injected with 500 MBq of (technetium-99m labelled pyrophosphate (^{99m}Tc-PYP) and two hours later further SPET imaging was undertaken to estimate infarct size. Apart from the different energy windows and imaging time the protocol on each day was identical. The single photon emission tomographic imaging was performed over 360°, 64 images being acquired and reconstruction being undertaken by back projection with a Butterworth filter to create sagittal, coronal, and transverse images. A study was regarded as positive when uptake could be clearly seen in all three views. In these studies all transverse slices for both indium-111 and ^{99m}Tc-PYP with uptake in the region of myocardium were then analysed by a semiautomatic programme that counted the number of volume cell elements (voxels) with values greater than 65% of the peak myocardial uptake.[18] For each patient it was possible to compare the volume of myocardium showing neutrophil uptake with the volume of infarcted myocardium as judged from the pyrophosphate images.

Patients also had a predischarge radionuclide ventriculogram to assess residual left ventricular function.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test showed that the data were not normally distributed. Results are therefore expressed as median and range. We used non-parametric analysis (Wilcoxon rank sum test) for two independent samples (Mann-Whitney). Values of $p < 0{\cdot}05$ were taken as significant and data were analysed by computer with the statistical package for social sciences (SPSS Inc, Chicago).

Results

WHITE BLOOD CELL COUNT

The white blood cell count was significantly lower in the normal volunteers (5·8 × 10^9/l, 3·4–9·3/l) than in patients with ischaemic heart disease without recent infarction (6·7 × 10^9/l, 5·2–12·6/l, $p < 0{\cdot}004$) and in both groups counts were lower than the initial white cell count in patients with acute myocardial infarction (16·4 × 10^9/l, 7·9–33·7, $p < 0{\cdot}0001$). This was also true for the neutrophil count for the three groups.

PLASMA NEUTROPHIL ELASTASE

The plasma concentration of neutrophil elastase was significantly lower in the normal volunteers (18·6 ng/ml, 9·2–51·0) than in the patients with stable ischaemic heart disease (25·8 ng/ml, 12·2–49·5, $p < 0{\cdot}002$). For the 48 hours after myocardial infarction, however, plasma neutrophil elastase was higher than in either normal volunteers or patients with ischaemic heart disease (fig 1a). The time course differed in patients who had received thrombolytic treatment and in those who had not.

PL-9, 11-LA' AND THE MOLAR RATIO PL-9, 11-LA'/PL-9, 12-LA

There was no significant difference in PL-9, 11-LA' or the molar ratio PL-9, 11-LA'/PL-9, 12-LA between normal volunteers (19·3 µmol/l, 7·5–32·9; 4·7, 1·9–9·1) and patients with ischaemic heart disease (19·8 µmol/l, 7·9–43·2; 5·4, 1·7–12·1). For the 48 hours after myocardial infarction PL-9, 11-LA' was significantly greater than in the healthy volunteers. The concentration reached a maximum at 16 hours; by 48 hours the values were not significantly greater than those of patients with chronic ischaemic heart disease (fig 1b). The molar ratio of PL-9, 11-LA'/PL-9, 12-LA was significantly increased in the 48 hours after myocardial infarction and followed a similar time course.

COMPARISON OF PATIENTS WITH MYOCARDIAL INFARCTION WHO WERE TREATED BY THROMBOLYSIS AND THOSE WHO WERE NOT

There was no significant difference in peak creatine kinase activity between patients treated conventionally and those who were treated by thrombolysis. Plasma activity of creatine kinase reached a peak earlier in those treated by thrombolysis (16 hours) than in those treated conventionally (24 hours). Similarly, there was no significant difference in the left ventricular ejection fraction measured by radionuclide ventriculography, 10 days after infarction, though those patients who were treated by thrombolysis had slightly higher values (table 1).

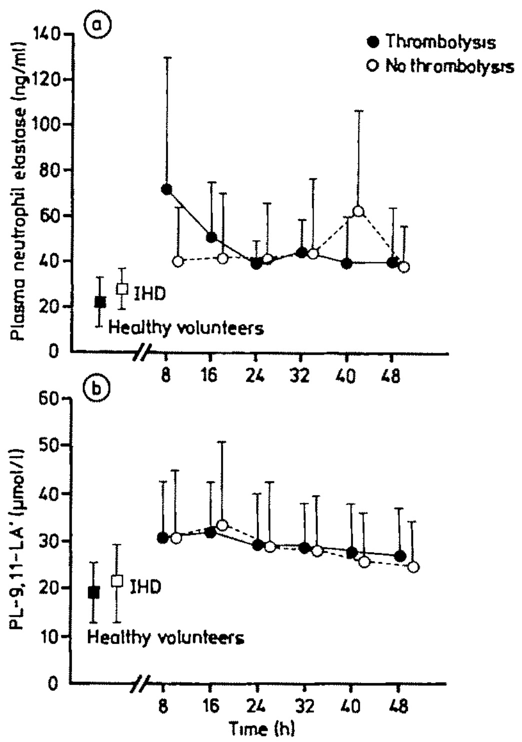

Figure 1 (a) Mean plasma neutrophil elastase (1 SD) in healthy volunteers, patients with chronic ischaemic heart disease (IHD), and those with acute myocardial infarction. Changes in plasma concentration neutrophil elastase (PNE) after myocardial infarction are shown for those treated with and without thrombolysis. The values of PNE are significantly greater at all sampling times after myocardial infarction than in healthy volunteers or patients with chronic ischaemic heart disease. Patients treated by thrombolysis have significantly higher values of PNE at 8 hours ($p < 0{\cdot}025$) and lower values at 40 hours ($p < 0{\cdot}037$) than those not treated by thrombolysis. (b) Mean PL-9, 11-LA' (1 SD) in the same groups showing significantly higher values after myocardial infarction than in ischaemic heart disease or in healthy volunteers. There was no difference between those treated by thrombolysis and those not treated by thrombolysis at any time.

PLASMA CONCENTRATIONS OF NEUTROPHIL ELASTASE

The pattern of change in plasma neutrophil elastase differed in the two groups of patients with acute myocardial infarction (fig 1a). Patients given intravenous thrombolysis had higher early maximal values at 8 hours (48·2 ng/ml, 25–250) than those treated conventionally (32·6 ng/ml, 15·6–101, $p < 0{\cdot}025$). Those treated conventionally tended to have lower early values with a late peak at 40 hours (49·8 ng/ml, 21·4–196) than those treated with thrombolysis (34·2 ng/ml, 15·8–83, $p < 0{\cdot}037$).

PL-9, 11-LA' AND THE MOLAR RATIO PL-9, 11-LA'/PL-9, 12-LA

There was no significant difference in PL-9, 11-LA' or the molar ratio PL-9, 11-LA'/PL-9, 12-LA in those treated conventionally after

Table 2 Details of patients treated with and without thrombolysis who were imaged with ^{111}In labelled neutrophils and ^{99m}Tc pyrophosphate

	CK max (U/l)	*LVEF (%)*	*Time to injection (h)*	*^{111}In (voxels)*	*^{99m}Tc (voxels)*	*^{111}In/^{99m}Tc*
No thrombolysis	2508	36	8	114	201	0·79
(n = 10)	(522–6255)	(15–51)	6·5–10	(19–276)	(77–405)	(0·06–2·14)
Thromolysis	2500	40	11	81	217	0·41
(n = 11)	(533–6955)	(27–68)	5–18	(0–160)	(111–323)	(0–0·96)
p	NS	NS	NS	NS	NS	<0·05

(Each voxel or volume picture cell element represents approximately 250 mm^3.)
CK, creatine kinase; LVEF, left ventricular ejection fraction

myocardial infarction and those given thrombolysis. For both groups the values were greatest at 16 hours, gradually falling towards normal values (fig 1b).

There was no correlation between the white blood cell count and plasma concentration of neutrophil elastase in any of the groups. There was a weak correlation between white cell count and PL-9, 11-LA' in the non-thrombolytic group ($r = 0·63$, $p < 0·02$), and in patients with ischaemic heart disease ($r = 0·45$, $p < 0·02$), but this did not hold for the corrected molar ratio and no correlations were found in the normal volunteers and patients treated with thrombolysis.

IMAGING (TABLE 2)

In general, in the patients who were imaged there was a significantly greater number of voxels showing an uptake of ^{99m}Tc pyrophosphate than of ^{111}In labelled neutrophils ($p < 0·0006$). Uptake of ^{99m}Tc pyrophosphate was very similar in patients who were treated by thrombolysis and those who were not, suggesting little difference in infarct size in these patients. This is supported by similar values of residual left ventricular ejection fraction and peak creatinine kinase in both groups (table 2). In contrast, the uptake of ^{111}In labelled neutrophils was less in the patients who were treated by thrombolysis. Thus the ratio of ^{111}In/^{99m}Tc, which serves as an estimate of the inflammatory response for a given infarct size, was significantly less in patients treated by thrombolysis (0·41, range 0–0·96) than in those treated without (0·79, range 0·06–2·14, $p < 0·05$). In fig 2 an example of the greater uptake of ^{111}In labelled neutrophils in a patient treated without thrombolysis is contrasted with that seen in a patient who had received streptokinase.

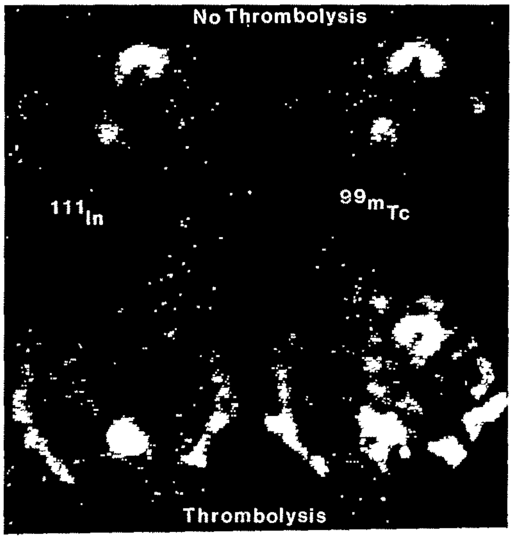

Figure 2 Single photon emission tomographic images comparing the uptake of ^{111}In labelled neutrophils with the size of infarction as assessed by ^{99m}Tc-pyrophosphate (PYP). The upper pair of images show easily detected uptake of ^{111}In and ^{99m}Tc-PYP in a patient with anterior myocardial infarction who was not given thrombolytic treatment. The lower pair of images show markedly reduced uptake of ^{111}In labelled neutrophils compared with ^{99m}Tc-PYP in a patient with anterior myocardial infarction treated with anistreplase

Discussion

We found both an increased neutrophil elastase release and an increase in the plasma concentrations of the diene conjugated non-peroxide isomer of linoleic acid (PL-9, 11-LA') after myocardial infarction. The association of leucocytosis and the severity of myocardial infarction was first described by White in 1926.[19] We noted increased neutrophil leucocytosis after myocardial infarction but there was no correlation between the peripheral neutrophil count and the raised plasma concentrations of neutrophil elastase. A distinction must be made between whole blood elastase and plasma elastase. Whole blood elastase correlates with the total neutrophil count but is not a marker of neutrophil activation and reflects the much greater intracellular stores of the enzyme. Increased plasma neutrophil elastase relates to neutrophil degranulation and presumably reflects release within the area of myocardial injury. The peripheral leucocytosis is part of the more general response to stress.[20] Like others we also noted an increased leucocyte count in patients with stable ischaemic heart disease and this has been shown to be a predictor of future myocardial events.[21] The neutrophil has been recognised as an early part of the inflammatory response to myocardial infarction,[22 23] but it is only more recently that experimental evidence has been put forward to suggest that it may be involved in secondary heterolytic myocyte damage after myocardial infarction[4 5] and that suppression of the neutrophil infiltrate can reduce infarct size.[2 3] One mechanism by which activated neutrophils can induce cell damage is through the release of potent proteolytic enzymes.

Neutrophil elastase is a serine protease released from the primary granules after major cell stimulation such as phagocytosis or cell death.[24] It has a wide range of substances including elastin, collagen, fibrinogen, and other matrix macromolecules and is implicated in the pathogenesis of several human diseases.[1] Our study showed that plasma concentrations of human neutrophil elastase were significantly higher in patients after myocardial infarction than in healthy volunteers and patients with stable ischaemic heart disease. Further, the pattern of elastase release was different in patients treated conventionally and in those treated with thrombolysis. In patients treated with streptokinase or anistreplase there was a significant early increase in plasma neutrophil elastase within the first few hours of treatment. This confirms previous observations[25] and it seems likely that this represents clot lysis or intracoronary activation of neutrophils because few inflammatory cells will have migrated into myocardial tissue by this stage.[22 23]

In contrast, in patients treated conventionally concentrations of neutrophil elastase reach a peak later, between 32 and 40 hours after the onset of symptoms, when the inflammatory infiltrate is present histologically and can be imaged.[17] Drug treatment, particularly hydrocortisone or lignocaine, might be expected to influence neutrophil behaviour. But a similar number of patients in both groups received lignocaine, which is known to depress neutrophil function in vitro.[26] Also patients given hydrocortisone before streptokinase did not have lower ^{111}In uptake by neutrophils or lower concentrations of elastase than patients treated with anistreplase, who did not receive hydrocortisone. This suggests that the results in the thrombolytic group are not influenced by the potential suppressive effect of hydrocortisone on the inflammatory response and neutrophil function.[27]

Although the neutrophil is a source of cytotoxic oxygen species, there are other potential sources of oxygen free radical production after myocardial infarction, including the conversion of xanthine dehydrogenase to xanthine oxidase, mitochondrial production, the auto-oxidation of catecholamines, and the arachidonic acid cascade.[8] Although xanthine dehydrogenase is converted to xanthine oxidase in the vascular endothelium, this enzyme system is not present in human myocytes and is therefore unlikely to be directly involved in myocardial damage.[28] Therefore, the most likely sources of free radical production within the human myocardium are the electron transport chains of the myocyte mitochondria or from activated neutrophils via the membrane linked nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidase.[10] Our studies of peripheral blood did not define the increase as being of myocardial origin, but the myocardium is the most likely site in patients who are haemodynamically stable.

Products of lipid peroxidation have been used as markers of free radical activity because exposure of cell membranes to oxygen free radicals stimulates "lipid peroxidation"[29]—perhaps better termed lipid oxidation. Lipid peroxidation products have themselves been implicated in damaging cell membranes after myocardial infarction,[30] though some have suggested that increased evidence of lipid peroxidation merely reflects cell damage.[15] For this reason we chose to measure the diene conjugated non-peroxide isomer of linoleic acid PL-9, 11-LA′ in plasma because this is thought to be a marker of human free radical activity.[16 31] PL-9, 11-LA′ is present in the diet and can be manufactured by bacterial flora and this may account for the conflicting reports of the usefulness of this as a marker of cervical cancer.[32 33] It is unlikely that changes in dietary intake or bacterial flora would alter significantly in the 48 hours after myocardial infarction to account for the changes seen in plasma PL-9, 11-LA′. Also the concentrations were not increased in the patients with stable, but documented ischaemic heart disease and there was no change in linoleic acid, which is also affected by dietary intake.

Heparin was shown to increase 9,11-LA′[34]—the assay method, which is designed to measure the molar concentration of 9,11-LA′and 9,12-LA esterified as phospholipids, also measures 9,11-LA′ and 9,12-LA present as free fatty acids. Free fatty acids are increased by the lipolytic action of heparin though the magnitude of the response is often overestimated because the method does not take account of the extensive ex-vivo lipolysis.[35] In our study heparin is unlikely to have had any significant effect because the thrombolytic group received only intravenous heparin as an adjuvant to thrombolysis a mean of 18 hours 36 minutes after the onset of symptoms. The patients treated conventionally also received heparin but as a low dose subcutaneously. We noted no difference in the values of PL-9, 11-LA′ between the two groups despite the widely different heparin regimens. The similarity of responses of the two groups also argues for a lack of effect of the thrombolytic drugs in themselves on PL-9, 11-LA′.

The concentration of PL-9, 11-LA′ or the molar ratio did not correlate with creatine kinase measured on the same sample and it therefore seems unlikely that the raised concentrations are merely a marker of cell damage[15] and the evidence is consistent with the diene being a free radical marker in human beings. In general, in patients with myocardial infarction the values of PL-9, 11-LA′ and the molar ratio were high initially and then fell; this suggests that maximum free radical generation occurs early. We were unable to detect any difference in the concentrations of PL-9, 11-LA′ or the molar ratio of PL-9, 11-LA′/PL-9, 12-LA between patients treated conventionally and those who received thrombolysis. This lack of difference in the molar ratio (indeed it was somewhat lower in the group treated by thrombolysis) suggests that reperfusion was not associated with a delayed or secondary increase in free radical production with the potential for further myocardial damage. Even when samples were taken earlier (less than 6 hours after the onset of symptoms) we did not detect any difference in those treated by thrombolysis. We cannot exclude the immediate increase in free radical production after reperfusion shown in some animal studies.[36] However, in human beings free radical injury after reperfusion may be reduced by the presence of red blood cells, which contain the antioxidant enzyme catalase[37] unlike the cell free perfusate often used in animal experiments.

This study confirms that the human inflammatory response to myocardial infarction can be imaged. In only two of the 21 patients studied no uptake of ^{111}In-labelled neutrophils could be detected. Both patients had been treated by thrombolysis and although this result could represent failed imaging, this is unlikely because all the thrombolytic group had significantly reduced uptake of neutrophils in relation to infarct size assessed by ^{99m}Tc-pyrophosphate. The concept of a reduced inflammatory response is supported by the different patterns of release of neutrophil elastase. If the early neutrophil activation in those given thrombolysis represents intracoronary activation and the late response corresponds to acute inflammatory infiltrate within damaged myocardium we would expect greater neutrophil uptake in those who did not receive thrombolytic agents. As an extension, the lack of a late increase in lipid oxidation suggests that the neutrophil is not the main source of free radical production in myocardial infarction. By inference this implies that if there is later heterolytic myocardial injury and if it is mediated by neutrophils, it may be secondary to release of proteolytic enzymes rather than oxygen free radicals. The results do not necessarily contradict the experimental evidence that suggests that free radical scavengers reduce myocardial damage,[36] because there is evidence that superoxide dismutase may work in part by reducing neutrophil migration.[38] It is therefore possible that some of the beneficial effects of thrombolysis are the result of partial inhibition of the inflammatory response to myocardial injury, perhaps by reducing the degree or duration of production of neutrophil chemoattractants, such as complement.[39 40]

Our studies suggest that after acute myocardial infarction neutrophils are activated and free radicals are produced. Although animal studies suggest such activation can extend myocardial injury we have no evidence of this in human beings. However, thrombolysis and presumed reperfusion are not associated with amplification of the inflammatory response or prolonged free radical production in patients. Indeed these responses seem to be diminished and some of the beneficial effects of thrombolysis may be the result of down regulation of the acute inflammatory response.

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Lipid peroxidation during myocardial ischaemia induced by pacing

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Abstract

Oxygen derived free radical generation can be shown in experimental models of myocardial ischaemia and reperfusion and may cause cellular damage by peroxidising polyunsaturated membrane phospholipids. An attempt was made to quantify human intracardiac lipid peroxidation during transient myocardial ischaemia by measuring the aortic and coronary sinus concentrations of malondialdehyde (a marker of lipid peroxidation) before, during, and after incremental pacing. Twenty six patients were paced until they had severe chest pain or 2 mm ST segment depression or they reached a paced rate of 180 beats/min. They were divided into two groups according to whether or not lactate was produced during pacing. Twelve patients (group 1), all with coronary artery disease, produced myocardial lactate during pacing. None of the other 14 patients (group 2), half of whom had coronary disease, produced lactate during pacing. Concentrations of malondialdehyde in the aorta and coronary sinus were significantly higher in group 1 than in group 2. Five minutes after the end of pacing coronary sinus malondialdehyde concentrations in group 1 had increased significantly from baseline values. There were no changes with time in the coronary sinus concentration of malondialdehyde in group 2 or in the aorta in either group. The negative malondialdehyde extraction ratio in group 1 suggests that intracardiac lipid peroxidation occurs during transient human myocardial ischaemia.

Electron paramagnetic resonance spectroscopy was used to provide direct evidence of oxygen derived free radical formation after coronary artery ligation in open chested dogs, but this involves the intracoronary infusion of a spin trap, in this case, α-phenyl *N-tert*-butyl nitrone and has not as yet been performed in humans.[1] The evidence implicating free radicals in the myocardial cell damage associated with myocardial ischaemia and particularly reperfusion is conflicting and rests largely on the results of studies of the use of various radical scavenging agents in animal models.[2 3] The enzyme superoxide dismutase, which scavenges free radicals, was shown to reduce infarct size in a canine model of coronary artery occlusion/reperfusion,[4] though this effect could not be reproduced by another group using a similar model.[5] Allopurinol, an inhibitor of the enzyme xanthine oxidase, which helps to generate free radicals, has been used in similar studies with the same conflicting results.[6 7] A problem common to all of this work is the difficulty of confirming an equal degree of ischaemia in each of the different treatment groups. Ambrosio *et al* tried to avoid this difficulty by quantifying the ischaemic insult using ^{31}P magnetic resonance spectroscopy to measure continuously myocardial phosphate content and intracellular pH. They were able to show that recombinant human superoxide dismutase accelerates the biochemical and functional recovery in isolated rabbit hearts subjected to periods of global ischaemia.[8]

Most animal models of ischaemia/reperfusion used periods of total global ischaemia. It is not known whether brief ischaemic insults without complete cessation of nutrient flow, such as occur during episodes of angina pectoris, also result in the generation of cytotoxic free radicals. As indicated above, direct measurement of the chemical moieties implicated (superoxide anion, hydroxyl radical) is difficult owing to their extremely short half lives. Free radical attack, however, causes the oxidative degradation of polyunsaturated lipids in cell and lysosomal membranes.[9 10] Among the products of this age and sex related lipid peroxidation,[11] various cytotoxic aldehydes have been characterised and shown to be, by themselves, capable of inducing changes within biological membranes.[12 13] One of these, malondialdehyde, can be measured in human plasma. We therefore measured concentrations of malondialdehyde and lactate in the aorta and coronary sinus before, during, and immediately after incremental cardiac pacing in patients with and without coronary artery disease.

Patients and methods

PATIENT SELECTION

We studied 26 patients (19 men) aged 42–68 undergoing cardiac catheterisation for the evaluation of chest pain. Patients with recently unstable angina were excluded. All drug treatment was continued until 24 hours before the study. Thereafter only sublingual nitrates were prescribed. Written informed consent was obtained from each subject and the study was approved by the ethics committee of Glasgow Royal Infirmary.

STUDY PROTOCOL

Patients fasted overnight and were sedated with diazepam (10 mg orally). Under local anaesthesia, disposable catheters were placed in the coronary sinus (via the left basilic vein) and the descending aorta (via the right femoral artery). A temporary pacing wire was placed in the right atrial appendage via the right femoral vein. The position of the coronary sinus catheter was confirmed by injecting a small amount of contrast medium. Arterial blood pressure and 12 electrocardiographic leads were monitored continuously throughout the study. Samples of arterial and coronary sinus blood were taken simultaneously to measure lactate and malondialdehyde.

The heart was then paced at just above the resting sinus rate and the rate was increased by 10 beats/minute every two minutes until the development of severe chest pain, 2 mm ST segment depression, or a paced rate of 180 beats/minute. If atrioventricular block developed before an end point was reached, the pacing wire was repositioned in the right ventricular apex and the study continued. Repeat arterial and coronary sinus blood samples were obtained at the peak pacing rate and at 30 seconds and five minutes (cases 10–26 only) after the end of pacing.

Individual variations in coronary venous anatomy, catheter placement, and the extent and pattern of coronary artery disease mean that biochemical changes in the coronary sinus effluent do not always reflect continuing myocardial ischaemia.[14] In an attempt to minimise this sampling error, and particularly in a study designed to show biochemical evidence of reperfusion injury, we decided to regard the response to incremental pacing as positive only when there was evidence of frank lactate production (that is, lactate concentration in the coronary sinus was higher than in the aorta). We used frank lactate production as the marker of an ischaemic response so that we could be as certain as possible that the sampling catheter was indeed draining an ischaemic area of myocardium.

ASSAYS

Lactate was measured by a commercially available enzymatic assay (Boehringer Diagnostica). Malondialdehyde was measured by the technique of Santos *et al.*[15] Plasma was separated immediately after each pacing study and all samples were assayed in duplicate on the same day. The mean intra and inter assay coefficients of variation in our laboratory are 5·0% and 7·7% respectively.

STATISTICAL ANALYSIS

The distribution of the data derived from this study was assessed by calculating the standardised skewness and kurtosis of each of the variables. Group concentrations are expressed as medians (inter-quartile range) for non-parametric data or means (SEM) for parametric data. Two tailed group comparisons were made by Wilcoxon signed rank and Mann-Whitney tests or Student's *t* test for paired and unpaired data as appropriate. Extraction ratios were calculated in the conventional manner from concentrations in the aorta and coronary sinus.

$$\frac{\text{Aorta} - \text{coronary sinus}}{\text{Aorta}} \times 100\%$$

Results

LACTATE EXTRACTION AND CORONARY ARTERY DISEASE

During pacing, myocardial lactate production developed or increased in 12 patients (group 1). The lactate extraction ratio, even at baseline, was significantly less in group 1 than in group 2 (lactate extractors): +18% (−7 to +29) *v* +40% (+25 to +45), $2p = 0\cdot01$. Despite the exclusion of patients with unstable or recently unstable angina, three patients in group 1 showed biochemical evidence of ischaemia at rest. By definition, all of the group 1 patients were producing lactate at peak pacing rate, while all 14 patients in group 2 continued to have a positive extraction ratio: −28% (−70 to −11) *v* +16% (+10 to +30).

Tables 1 and 2 summarise the clinical and anatomical characteristics of the patients in both groups. The groups were comparable for age and sex (mean ages, 56 *v* 54; men, 8/12 *v* 10/14). All 12 patients in group 1 had obstructive coronary artery disease, including in 10 patients a stenosis of at least 50% (diameter) in the left anterior descending artery. Patients 6 and 7 did not have disease of the left anterior descending artery but did develop evidence of ischaemia in the anterolateral leads during exercise and pacing. In half of the patients in group 2, the results of coronary angiography

Table 1 Clinical and anatomical characteristics of lactate producers (group 1)

Case no	Age	Sex	Treatment	Peak paced heart rate (beats/min)	ST depression (≥1·0 mm) Exercise	ST depression (≥1·0 mm) Pacing	CAD	Left ventricle
1	60	M	Ca, nitrate	180	II, III, aVF, V4–6	II, III, aVF, V4–6	3VD	Abnormal
2	52	M	BB, Ca, nitrate	130	V3–5	V3–6	3VD	Normal
3	51	M	BB, Ca, Asp	110	II, III, aVF, V4–6	II, III, aVF, V4–6	3VD	Abnormal
4	57	M	Nil	170	V2–5	V2–6	LAD	Normal
5	60	F	BB, Ca, Asp	170	II, III, aVF, V4–6	II, III, aVF, V4–6	LAD	Normal
6	64	M	BB, Ca, Asp	120	V2–6	V2–6	RCA	Normal
7	60	M	BB	140	I, II, aVL, V4–6	I, II, aVL, V4–6	RCA, Cx	Normal
8	58	M	BB, nitrate	150	V2–4	V2–4	3VD	Abnormal
9	64	F	BB	150	I, aVL, V2–6	I, aVL, V3–6	3VD	Normal
10	43	M	BB, Ca, nitrate	170	V1–4	V1–4	LAD	Normal
11	59	F	BB, Ca, nitrate	150	I, aVL, V2–6	I, aVL, V2–6	LAD, RCA	Abnormal
12	53	M	BB, nitrate	160	II, III, aVF, V3–5	II, III, aVF, V4–6	LAD, Cx	Normal

CAD, coronary artery disease (≥50% diameter stenosis); 3VD, 3 vessel disease; LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex; Ca, calcium antagonist; BB, β blocker; Asp, aspirin.

Table 2 Clinical and anatomical characteristics of lactate extractors (group 2)

Case no	*Age*	*Sex*	*Treatment*	*Peak paced heart rate*	*ST depression ($\geqslant 1·0$ mm)*		*CAD*	*Left ventricle*
					Exercise	*Pacing*		
1	61	M	BB, nitrate, Asp	140	I, II, aVL, V2–6	I, II, aVL, V2–6	3VD	Normal
2	49	F	Nil	160	II, III, aVF, V4–6	V2–6	Nil	Normal
3	49	M	Nil	150	I, aVL, V5–6	V5–6	3VD	Abnormal
4	51	F	BB, nitrate	150	Nil	II, III, aVF, V3–5	Nil	Normal
5	51	M	BB, Ca, nitrate	120	II, III, aVF, V4–6	II, III, aVF, V5–6	3VD	Normal
6	47	F	Nil	180	Nil	II, III, aVF, V3–6	Nil	Normal
7	53	M	Ca, Asp	140	Nil	Nil	Nil	Normal
8	50	F	Ca, nitrate	160	Nil	Nil	Nil	Normal
9	50	M	BB	160	Nil	Nil	Nil	Normal
10	65	M	Ca, nitrate	150	II, III, aVF, V3–6	I, II, V4–6	3VD	Normal
11	63	M	Nil	160	V2–5	I, aVL, V3–6	Nil	Normal
12	55	M	BB, nitrate	180	Nil	Nil	LAD, RCA	Abnormal
13	68	M	BB, nitrate	150	II, III, aVF, V5–6	V3–6	3VD	Normal
14	53	M	BB, nitrate, Asp	170	Nil	Nil	3VD	Abnormal

See footnote to table 1 for abbreviations

were normal. The other seven had coronary artery disease; in all seven there were major lesions in dominant right coronary arteries. In two of these seven patients there was no electrical evidence of ischaemia on exercise or pacing. Four of the other five showed ischaemia only in the inferior or inferolateral leads. The venous drainage from the myocardium supplied by the right coronary artery usually drains into the proximal coronary sinus, and in patients with rate-limiting right coronary artery stenoses the sampling catheter may not accurately reflect ischaemia in the territory of the right coronary artery.[14] This may partly account for our failure to detect lactate production in these seven patients. The only patient in group 2 who had coronary disease and electrical evidence of anterior ischaemia during pacing (patient 1, ST depression >1 mm in leads I, II, aVL, V2-6) had complete occlusion of the right coronary artery.

PLASMA CONCENTRATIONS OF MALONDIALDEHYDE DURING PACING

Malondialdehyde concentrations before pacing, like the basal lactate extraction, were significantly higher in group 1 (lactate producers) than in group 2 (lactate extractors) in both the aorta and coronary sinus (table 3). The values in group 1 but not in group 2 were significantly higher than the peripheral venous blood concentrations in a group of 16 normal subjects (18·5 (1·4) μmol/l: $2p = 0·004$ *v* aorta, $2p = 0·006$ *v* coronary sinus). At all three subsequent sampling times, except in the aorta 5 minutes after pacing, this difference was maintained. Additionally, 5 minutes after pacing there was a significant increase in coronary sinus concentrations in group 1 after the end of pacing compared with baseline (fig 1). In contrast, there were no significant changes with time in the coronary sinus concentrations in group 2 or in the aorta in either group. This resulted in the generation of a negative malondialdehyde extraction ratio 5 minutes after pacing in group 1 that differed significantly from the positive ratio present in group 2 at the same time (fig 2).

Discussion

Incremental pacing to provoke myocardial ischaemia in resting patients with coronary artery disease partly avoids the complicating and unpredictable systemic metabolic effects of exercise stress.[16] Because pacing produces regional rather than global ischaemia, however, problems remain with the assessment of biochemical changes in ischaemic myocardium by sampling of the coronary effluent. Thus large changes in the ischaemic area may be masked by the diluting effect of venous effluent from non-ischaemic areas.[14 17] We chose to sample 30 seconds after the end of pacing because this is the time of maximum washout of toxic ischaemic metabolites from the myocardium.[18] The sample taken 5 minutes after pacing was added to try to identify lipid peroxidation occurring as a result of continuing reoxygenation of the previously ischaemic heart.

There are several potential sources of oxygen derived free radicals during human myocardial ischaemia/reperfusion. Ischaemia itself may produce cytotoxic free radicals as a result of reactions involving mitochondrial electron transfer[19] or after catecholamine degradation by monoamine oxidases, auto-oxidation or, what is more likely at physiological pH, metal catalysed oxidation.[20 21] The univalent reduction of oxygen by activated neutrophils, though an important source of radicals[20 22] is probably not relevant in transient ischaemia, because it is likely that the chemotactic factors required to promote neutrophil migration into ischaemic tissue require several hours for full expression.[23] In separate studies, we found no

Table 3 Plasma concentrations of malondialdehyde during pacing (μmol/l)

	Aorta			*Coronary sinus*		
	Group 1	*Group 2*	*95% CI†*	*Group 1*	*Group 2*	*95% CI†*
Baseline	26·2 (1·9)*	20·4 (1·8)	0·4–12·0	25·6 (1·6)*	20·6 (1·6)	0·1–10·0
Peak heart rate	26·0 (1·9)*	20·4 (1·7)	0·2–12·0	26·2 (1·5)*	20·4 (1·5)	1·2–10·0
30 s post pacing	25·4 (1·5)*	20·2 (1·5)	0·8–10·0	28·2 (2·2)*	20·4 (1·8)	1·8–14·0
5 min post pacing	26·6 (2·4)	23·2 (2·2)	−0·4–10·0	29·2 (1·8)*	21·8 (2·4)	1·0–14·0

*$2p < 0·05$ compared with group 2

†95% confidence intervals for the difference in mean values (unequal variance)

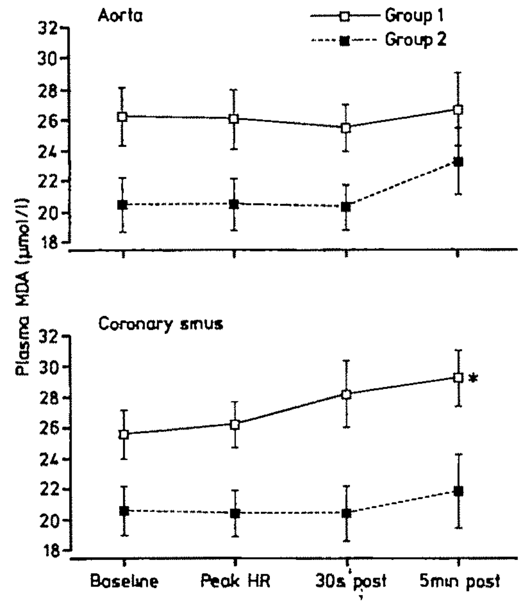

*Figure 1 Plasma concentrations of aortic and coronary sinus malondialdehyde during pacing. *2p < 0 05 compared with baseline. MDA, malondialdehyde; HR, heart rate.*

evidence of granulocyte activation as measured by aggregation after pacing induced ischaemia (unpublished observations). Reperfusion accelerates the production of oxygen derived free radicals by supplying a large substrate pool of molecular oxygen. The action of endothelial xanthine oxidase on purine metabolites accumulated during ischaemia is another possible system for generating radicals,[1,22] though its relevance has been questioned by workers who were unable to show significant xanthine oxidase activity in human myocardium.[24,25] Whatever their source, these oxygen radicals peroxidise polyunsaturated membrane lipids, damaging their structure and function, a process which in itself generates further free radicals.[6] Additionally, the activity of superoxide dismutase and glutathione peroxidase, two major mammalian intracellular radical scavengers, is reduced by hypoxia.[26,27] So free radical mediated cell damage is possible during any sequence of ischaemia/reperfusion and there is also at least some potential for autocatalysis/self-perpetuation.

Malondialdehyde is one of many products of lipid peroxidation. The reaction between thiobarbituric acid and malondialdehyde produces a pink colour which can be measured by spectrophotometry. This assay has been used to study circulating lipoperoxides in many diseases.[15,28,29] The particular variation of the assay that we used gives higher values than those reported for other methods because it measures both pre-existing malondialdehyde plus whatever other substances give rise to malondialdehyde during the assay—that is in vitro and in vivo.[15] In addition, several chemical species other than malondialdehyde can react with thiobarbituric acid to produce a pink to red colour.[30] This relative lack of specificity has been criticised, but malondialdehyde does seem to be produced in relatively constant proportion to the rate of lipid peroxidation,[31] and thus when all the samples from one patient are assayed simultaneously the results should reflect the degree of peroxidation at the time each sample was obtained.

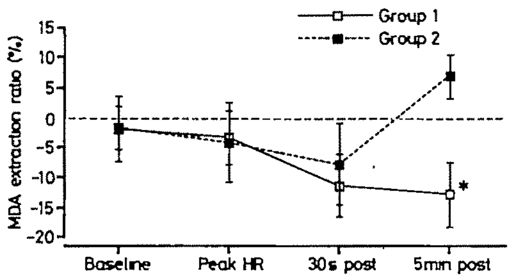

*Figure 2 Malondialdehyde extraction ratios during pacing. *2p < 0·05 compared with group 2. See legend to fig 1 for abbreviations.*

We showed that patients with coronary artery disease who produce lactate across the myocardium during incremental cardiac pacing also show an increase in the coronary sinus concentration of malondialdehyde in the period immediately after pacing. These latter changes may develop as early as 30 seconds after pacing and persist for at least 5 minutes. They did not occur in patients who, irrespective of the presence of coronary artery disease, continued to extract lactate during incremental pacing. The time course of these changes is consistent with the hypothesis that intracardiac lipid peroxidation occurs even after brief periods of regional myocardial ischaemia, possibly as part of reoxygenation injury mediated by free radicals. For the technical reasons outlined above we may have underestimated the true degree of intra-myocardial lipid peroxidation.

The clinical relevance of the small though none the less statistically significant changes we did detect remains unclear. As indicated earlier, it has not been possible to show consistently the theoretically beneficial effects of radical scavenging interventions in animal models of myocardial ischaemia.[2-8] Differences in the dosage and time course of administration of the agents used, and in the duration of occlusion/reperfusion may account for some of the variability in the results of these studies. In any case, the inability to modify ischaemic/reperfusion damage with such interventions does not necessarily mean that free radicals are without pathogenetic significance. Indeed, lipid peroxides are known to be prothrombotic through effects on the coagulation system[32] and platelets,[33] and this could clearly have a role in coronary heart disease.[34] Furthermore, the persistence of regional left ventricular dysfunction ("myocardial stunning") for several hours after brief (<20 minutes) periods of coronary artery occlusion[35] and the same phenomenon after exercise induced and completely reversible myocardial ischaemia in dogs,[36] may be the result of membrane lipid peroxidation mediated by free radicals.[20] If this could be confirmed in humans, and the source of the free radicals identified, the way would be open for a thorough exploration of the potential therapeutic role of free radical scavenging agents and antioxidants in both acute and chronic ischaemic syndromes.

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Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance

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Abstract

Cardiac output measured by thermodilution in 25 patients within 24 hours of acute myocardial infarction was compared with cardiac output measured by Doppler echocardiography (24 patients) and electrical bioimpedance (25 patients). The mean (range) cardiac outputs measured by Doppler (4·03 (2·2–6·0) l/min) and electrical bioimpedance (3·79 (1·1–6·2) l/min) were similar to the mean thermodilution value (3·95 (2·1–6·2) l/min). Both non-invasive techniques agreed closely with thermodilution in most patients. None the less, three results with each method disagreed with thermodilution by more than 1 l/min.

Both non-invasive techniques were reproducible and accurate in most patients with acute myocardial infarction. Doppler echocardiography was time consuming and technically demanding. Electrical bioimpedance was simple to use and had the additional advantage of allowing continuous monitoring of the cardiac output.

Knowledge of the cardiac output is valuable in the management of patients with acute myocardial infarction because it identifies patients at greatly increased risk and also provides a rapid means of monitoring the response to treatment.[1] Most patients, however, are managed without measurement of cardiac output—by relying on clinical signs. Unfortunately these can be misleading in this group of patients. Arterial blood pressure may be maintained in the face of a low cardiac output by raised systemic vascular resistance. A fall in urine output is an indication of reduced renal blood flow, but this may be due to activation of the sympathetic nervous system and does not necessarily indicate a low cardiac output.[2] The chest *x* ray is a sensitive indicator of raised left atrial pressure,[2] but measurement of cardiac output has until recently required right heart catheterisation. An accurate non-invasive method of measuring cardiac output would therefore have many attractions: two of the most promising techniques are Doppler echocardiography and electrical bioimpedance.

Although a high degree of accuracy has been claimed for both methods,[3–7] all of these studies were conducted in normal volunteers subjected to various artificial means of altering cardiac output or in patients in intensive care with a wide range of haemodynamic disturbances. None of the previous studies of electrical bioimpedance and only one study of Doppler included patients with acute myocardial infarction.[3]

A new bioimpedance monitor (BoMed NCCOM3) has recently been developed that simplifies the measurement of cardiac output. We wished to compare the accuracy of this new monitor with Doppler echocardiography in acute myocardial infarction. It is not possible to extrapolate from results obtained in normal volunteers during exercise or patients in general intensive care because patients with myocardial infarction may have much lower cardiac outputs.

The aims of this study were to assess the feasibility, reproducibility, and ease of use of both non-invasive techniques in patients with recent (<24 hours) myocardial infarction and to compare cardiac output determined by Doppler echocardiography and electrical bioimpedance with that obtained by thermodilution in the same patients.

Patients and methods

PATIENTS

We studied men and women aged <75 years admitted to our coronary care unit with a diagnosis of acute myocardial infarction. All patients were studied within 24 hours of the onset of chest pain. Patients were included in the study if there was a clinical indication for Swan-Ganz catheterisation (early heart failure, hypotension, or poor urine output).

Patients were excluded if they had any condition known to interfere with the bioimpedance signal such as obesity or pleural effusion. An initial screening echocardiographic study was performed to exclude patients with significant aortic valve disease, tricuspid incompetence, or pericardial effusion.

SWAN-GANZ CATHETERISATION

A 7F, triple lumen, Edwards Laboratories Swan-Ganz catheter was advanced from an antecubital vein to the pulmonary artery under fluoroscopic control. Intracardiac and pulmonary artery pressures were recorded and patients were then returned to coronary care. Thermodilution cardiac output was measured by an Edwards Laboratories cardiac output computer with 10 ml iced dextrose. The mean of three injections, all within 10% of each other and excluding the first injection, was recorded. It was not possible to perform all three techniques simultaneously because the bioimpedance monitor interferes with the Doppler signal. Therefore, Doppler recordings of aortic

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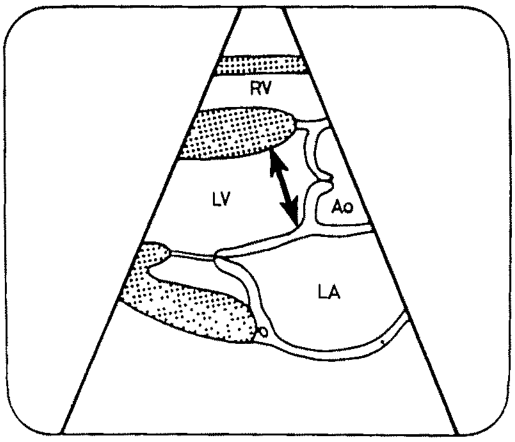

Figure 1 Echocardiographic measurement of the diameter of the left ventricular outflow tract. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle

flow were recorded immediately before or immediately after the other two techniques.

DOPPLER ECHOCARDIOGRAPHY

The diameter of the left ventricular outflow tract was used to calculate the cross sectional area, assuming a circular profile. Measurements were made by cross sectional echocardiography in the parasternal long axis view (Hewlett Packard model 77020A with a 2·5 MHz phased array transducer). With the image frozen in midsystole, the diameter of the left ventricular outflow tract was measured immediately proximal to the aortic valve leaflets as described by Lewis *et al.*[5] We calculated the diameter as the mean of five measurements using the trailing-edge to leading-edge method (fig 1).

We measured aortic blood velocity by continuous wave Doppler ultrasound using a small 1·9 MHz probe and the same Hewlett Packard system. Care was taken to obtain the clearest spectral profile from both the suprasternal and apical windows. When both windows were successful the site giving the highest aortic flow velocities was used for analysis, as described by Bouchard *et al.*[6] No attempt was made to measure and correct for the angle between the continuous wave Doppler ultrasound beam and the direction of blood flow. We took hard copies on a strip chart recorder and analysed them off line using a Kontron computer and magnetised digitising tablet. Stroke distance was taken as the mean of 10 measurements of the area under the time velocity curve. Doppler cardiac output was calculated as:

$$CO = SD \times CSA \times HR$$

where SD was stroke distance and CSA was the cross sectional area of left ventricular outflow tract.

The stroke distance was compared with stroke volume index to determine whether measurement of the cross sectional area was necessary (SVI = thermodilution CO/body surface area).

ELECTRICAL BIOIMPEDANCE

After skin preparation the bioimpedance monitor was connected to the patients via four pairs of low contact impedance electrodes. The lower thoracic voltage sensing electrodes were placed at the level of the xiphoid sternum in the midaxillary lines and the cervical sensing electrodes were positioned laterally at the base of the neck as close as possible to the clavicles. The "current injecting" electrodes delivered an alternating current at 70 kHz and were placed with one pair 5 cm above the cervical sensing electrodes and the other pair 5 cm below the thoracic sensing electrodes. The BoMed NCCOM3 estimated stroke volume from the impedance signal recorded from the inner pairs of electrodes using the Stramek *et al* equation.[7]

$$SV = VEPT \times VET \times (dz/dt)max/Z0$$

Where VEPT = volume of electrically participating tissue (a constant derived from body height and weight); VET = ventricular ejection time; dz/dt = rate of change of impedance during systole; and Z0 = basal thoracic impedance.

The monitor automatically averages stroke volume over twelve cardiac cycles and displays the cardiac output continuously. Electrical bioimpedance cardiac output was taken simultaneously with thermodilution measurements as the mean of 10 displayed values (that is the mean of 120 cardiac cycles). To investigate the accuracy of bioimpedance measurements without the influence of body size or heart rate, we also compared the stroke volume index measured by electrical bioimpedance with that measured by thermodilution.[8]

REPRODUCIBILITY

A pilot study was performed to measure the reproducibility of each non-invasive technique. Ten patients were studied who were all haemodynamically stable in the recovery phase after myocardial infarction. The bioimpedance monitor was applied as described above, and cross sectional echocardiography and Doppler studies were recorded on videotape. After 30 minutes' rest (to allow time for the electrode skin marks to disappear) the bioimpedance monitor was reapplied and a second cardiac output was recorded. Doppler echocardiography was performed a second time, by the same observer, and recorded on a separate videotape. The two tapes were analysed four weeks apart.

The coefficient of variation for repeat measurements by the same observer using electrical bioimpedance was 2·7%. The variability of echocardiographic measurement of aortic diameter was 1·5% and of the Doppler stroke distance 3·0%. Thus the variability of Doppler echocardiographic measurements was greater than electrical bioimpedance, since the square of the aortic dimension is multiplied by the stroke distance in the calculation of cardiac output.

STATISTICS

Cardiac outputs measured by the different techniques were compared by the method of Bland and Altman.[9] The intra-observer variability of the non-invasive methods was calculated as the coefficient of variation. Means were compared by Student's paired *t* tests, and a p value $<0·05$ was regarded as significant.

Results

PATIENTS

During the 10 month study, 29 patients had a Swan-Ganz catheter inserted within 24 hours of myocardial infarction. Four were excluded from the study because of aortic valve disease (two patients), severe obesity (one patient), or inadequate visualisation of left ventricular outflow tract on screening echocardiographic study (one patient). Therefore 25 patients (22 men), mean age 59 (range 47–72) years, were recruited and an attempt was made to measure cardiac output by all three techniques in every patient. This was successful in all but one patient, who was not suitable for Doppler echocardiographic examination (see below). The mean interval from the onset of pain to inclusion in the study was 16 hours 24 minutes. Acute myocardial infarction was confirmed subsequently by typical electrocardiographic changes and a rise in cardiac enzymes in all patients.

DOPPLER CARDIAC OUTPUT VERSUS THERMODILUTION

Cardiac output was measured by Doppler echocardiography in 24 patients; in one patient it was not possible to obtain a clear recording of aortic flow from either the apical or the suprasternal window. The mean (range) cardiac output by Doppler was 4·03 (2·2–6·0) l/min, which was not significantly different from the mean cardiac output by thermodilution, 3·95 (2·1–6·2) l/min (p = 0·72).

Analysis of the results by the method of Bland and Altman[9] (fig 2) gave the 95% limits of agreement as − 1 23 to + 1·32 l/min (−31% to +33% of the mean cardiac output). In three patients the Doppler result differed from thermodilution by more than 1 l/min.

ELECTRICAL BIOIMPEDANCE VERSUS THERMODILUTION

The mean (range) cardiac output by electical bioimpedance in 25 patients was 3·79 (1·1–6·2) l/min, which did not differ significantly from thermodilution at 3·95 (2·1–6·2) l/min (p = 0·22). The 95% limits of agreement (fig 3) were − 1·43 to + 1·11 l/min (−36% to +28% of the mean cardiac output). In three patients the electrical bioimpedance result differed from thermodilution by more than 1 l/min.

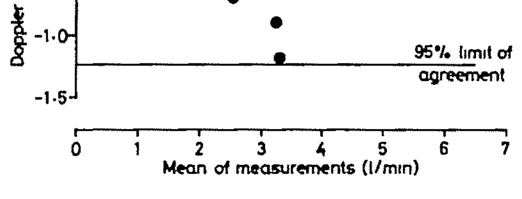

Figure 2 Difference between Doppler and thermodilution measurements of cardiac output plotted against the mean value.

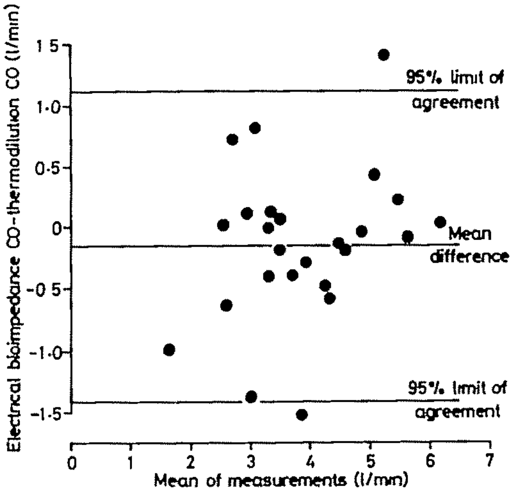

Figure 3 Difference between electrical bioimpedance and thermodilution measurements of cardiac output plotted against the mean value.

DOPPLER AND ELECTRICAL BIOIMPEDANCE MEASUREMENTS OF STROKE VOLUME INDEX

The mean (range) stroke distance by Doppler was 14·3 (4·3–21·7) cm. When compared with thermodilution measurements of stroke volume index the correlation coefficient was 0·82; SD = 0·43 × SVI + 3·38. Stroke volume index was also calculated from the bioimpedance measurements. The 95% limits of agreement with thermodilution were −8·1 to +6·7 ml/m².

Discussion

To our knowledge this is the first reported study of the accuracy of electrical bioimpedance in patients with acute myocardial infarction, and only the second study of Doppler echocardiography.[3] Previous reports compared Doppler determination of cardiac output with an invasive technique in other clinical settings. These studies, however, varied greatly in the numbers and types of patients studied, the number of observations per subject, the invasive technique used for comparison, and the Doppler method used. Good results were obtained with both pulsed and continuous wave Doppler, with sampling of flows in the aortic root, ascending aorta, descending aorta (including transoesophageal approach) and across the mitral, tricuspid, or pulmonary valves,[10–12] but the results of different studies were variable. Three important studies compared the accuracy of these various Doppler sites in the same patients, and found the ascending aorta and left ventricular outflow methods to be the most accurate.[5 11 12] Similar comparisons showed that of the many aortic diameters that can be used in the calculations the aortic annulus or left ventricular outflow tract gives the best results, and when the ascending aortic root is used there is considerable overestimation of cardiac output.[5 6 13] It was possible to obtain measurements of aortic flow from either the suprasternal or apical window in >90% of patients in a previous large study.[11] We also found that this was the case in 24 of our 25 patients, and when both sites were successfully studied the apical window gave the highest peak velocity in every case.

In the only previous study of Doppler measurements in acute myocardial infarction the methods used were comparable with our study, and the technique was feasible in all patients. It was also thought to be accurate, with a reported correlation coefficient of 0·95.[3] These workers, in common with most previous studies, investigated the agreement between the Doppler and invasive results solely by using the correlation coefficient. This is not a good method of determining the accuracy of a test or of comparing the results of one study with another.[9,14] It can be considerably affected by a few reasonably accurate results at the extremes of a range of measurements and it is dependent upon the range under study (when cardiac output is studied the range depends upon the types of patients included). This may explain why studies in which cardiac outputs have varied by up to 20 fold have produced coefficients as high as 0·98.[15] We used the method of Bland and Altman to assess the accuracy of the technique.[9,14,16] This statistical method is not affected by the range under study or values at the extremes of the measurement, and it has the added advantage of expressing the results in a clinically meaningful manner. Using this method we showed that Doppler may overestimate the thermodilution cardiac output by up to 1·3 l/min, or underestimate it by up to 1·2 l/min. Thus for 95% of measurements the thermodilution result would lie between 1·3 l/min below and 1·2 l/min above a single Doppler estimate. The magnitude of these errors did not depend upon the absolute cardiac output, so they are potentially much more of a problem in patients with low cardiac outputs. For instance, a result of 3 l/min by either non-invasive technique may under or overestimate the thermodilution result by 37–47%, whereas for a result of 6 l/min the error lies between 18% and 23%.

Stroke distance measured by Doppler does not have the same units as stroke volume index measured by thermodilution, and because different variables were being compared we used regression analysis rather than the method of Bland and Altman. Regression analysis showed a close correlation ($r = 0{\cdot}82$), which lends support to the adoption of stroke distance as a measure of cardiovascular function, as proposed by Haites *et al.*[17] It is also important in practical terms because stroke distance can be measured by inexpensive "stand alone" Doppler equipment without the need for imaging. This is an interesting additional finding in a study designed primarily to investigate the measurement of cardiac output not stroke distance.

Interest has been aroused in electrical bioimpedance by the recent development of the new bioimpedance monitor (BoMed NCCOM3) used in this study.[8,19] A review of the published reports showed nine previous studies in adults in which this monitor was compared with thermodilution. All were conducted in intensive care, usually on patients after general surgery. Once again it is difficult to compare our results with previous reports because they have all relied on correlation coefficients to describe the accuracy of bioimpedance. None the less, our results seem to be broadly in keeping with previous experience.[20,21] We found that the cardiac output by thermodilution is likely to lie within a range from 1·1 l/min below to 1·4 l/min above a bioimpedance estimate. The high degree of reproducibility of electrical bioimpedance measurements in this study was also reported by others.[19] In the largest series described so far, electrical bioimpedance could be measured in all of 58 critically ill patients after general surgery.[22] Only one previous study has compared both Doppler and bioimpedance measurements with thermodilution, and this was conducted in an intensive care unit.[20] Both techniques were feasible in >85% of patients and, in keeping with our findings, bioimpedance was slightly more accurate than Doppler though the difference was not statistically significant.

Cardiac output is the product of stroke volume and heart rate and under normal conditions stroke volume is related to body surface area. Spurious associations can therefore be generated when cardiac output is calculated by a method, such as electrical bioimpedance, that incorporates both heart rate and body surface area in its formula.[8] Indeed older bioimpedance monitors were unable reliably to determine stroke volume index,[23] and estimated cardiac output mainly from the patient's size and heart rate. A recent study found that although cardiac output determined by the BoMed NCCOM3 correlated with indirect Fick measurements, this relation was no longer significant when stroke volume index was used instead of cardiac output.[19] We therefore compared stroke volume index measured by electrical bioimpedance with thermodilution, and found that the 95% limits of agreement were −8·1 to +6·7 ml/m^2 (−32·4% to +26·8% of the mean stroke volume index). Thus electrical bioimpedance measurement of stroke volume index was just as accurate as the measurement of cardiac output. This study differs from the previous one,[19] in which healthy volunteers were studied. Large changes in cardiac output were induced by maximal exercise such that a correlation was found between the two non-invasive techniques even though individual measurements varied widely. Because the increase in cardiac output that accompanies exercise is produced mainly by an increase in heart rate,[24] a relatively smaller range of stroke volumes were studied. It is, therefore, not surprising that the correlation is less strong. A further problem with this study is that bioimpedance was compared with indirect Fick measurement of cardiac output rather than an invasive method. We used thermodilution as a "gold standard," and although we accept that this technique is far from perfect it is an established reference technique.

We found that both non-invasive techniques were feasible in patients with acute myocardial infarction. Doppler echocardiography required a lot of practice and the system we used took approximately 30 minutes to analyse each measurement. Electrical bioimpedance was highly reproducible, simple to use, and gave instant results. It has the additional advantage of allowing continuous monitoring of the cardiac output, which can be helpful in assessing the response to treatment.

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Optimal value of filling pressure in the right side of the heart in acute right ventricular infarction

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Abstract

Haemodynamic monitoring was performed within the first 48 hours after the onset of symptoms in basal conditions, during volume loading, and during infusion of glyceryl trinitrate in 41 patients who fulfilled the diagnostic electrocardiographic and haemodynamic criteria of right ventricular infarction. In most patients an increase of mean right atrial pressure up to 10–14 mm Hg was followed by an increase in right ventricular stroke work index. But raising the mean right atrial pressure above 14 mm Hg was almost always accompanied by a reduction in right ventricular stroke work index. When the mean right atrial pressure was reduced by intravenous glyceryl trinitrate to <14 mm Hg the right ventricular stroke index increased. The same response was seen with cardiac and stroke index. The mean (SD) values of optimal right atrial and pulmonary capillary pressures were 11·7 (2·1) and 16·5 (2·7) mm Hg respectively.

Thus cardiac and stroke index increased and the right ventricle reached its maximum stroke work index when the filling pressure was 10–14 mm Hg. These values may be regarded as the optimal level of right ventricular filling pressure in patients with right ventricular infarction.

The ventricular filling pressure in patients with acute myocardial infarction has been the subject of a series of haemodynamic studies.[1-3] The optimal value of left ventricular filling pressure during acute myocardial infarction has been known for many years. Studies on optimal filling pressure of the right ventricle in patients with right ventricular infarction are, however, few and not conclusive.[3 4] In fact, in one of them the true incidence of right ventricular infarction in the patients who were studied was not known.[3] Others have studied only one subgroup of patients with right ventricular infarction and a cardiac index of < 2·2 l/min/m^2,[4] whereas the range of values in this syndrome is wide.

This study was designed to establish the optimal value of right ventricular filling pressure in patients with right ventricular infarction.

Patients and methods

Forty one (36 men and five women, mean (SD) age 56·3 (7·4)) of the 106 patients admitted to the coronary care unit between February 1986 and March 1988 with a first acute inferior or posteroinferior myocardial infarction fulfilled the diagnostic electrocardiographic and haemodynamic criteria of right ventricular infarction and were the subject of this study. The diagnosis of inferior myocardial infarction was established by the presence of: (*a*) a positive clinical history; (*b*) a diagnostic increase in serum enzymes and (*c*) abnormal Q waves in leads II, III, and aVF.

The diagnosis of right ventricular infarction was established by the presence of the following electrocardiographic and haemodynamic findings: (*a*) ST segment elevation $\geqslant 1$ mm in leads V3R–V4R or (*b*) QS or QR waves or both in the same leads; (*c*) mean right atrial pressure > 10 mm Hg and greater than, equal to, or not more than 5 mm Hg lower than pulmonary capillary pressure (in basal conditions or after volume loading). We chose these criteria because they have a diagnostic specificity of 95–100% and a high sensitivity.[5-7] We excluded from the study all the patients with a difference of >5 mm Hg between pulmonary capillary pressure and pulmonary artery diastolic pressure; those with previous myocardial infarction or other diseases such as valvar heart disease, percarditis, pulmonary embolism, left to right shunt, chronic heart failure, and renal insufficiency; and all the patients with a pulmonary capillary pressure >20 mm Hg.

HAEMODYNAMIC VARIABLES

After informed consent was obtained from the patient a Swan-Ganz thermodilution catheter was placed in the pulmonary artery within the first 48 hours after the onset of symptoms. Right atrial, right ventricular, and pulmonary artery pressures were recorded with a Bentley Trantec Model 800 transducer on a CGR 1000 apparatus. Cardiac output was determined by thermodilution by an Edwards 9520A computer and the average value of three measurements showing a difference of <10% was calculated. Heart rate was derived from the electrocardiographic recordings. Arterial pressure was measured with a sphygmomanometer. The haemodynamic indices were calculated according to the following formulas: $CI = CO/BSA$ (where CI is cardiac index in l/min/m^2, CO is cardiac output in l/min, and BSA is body surface area in m^2); $SI = CI/HR \times 1000$ (where SI is stroke index in ml/beat/m^2 and HR is heart rate in beats/min); $RVSWI = SI \times (MPAP - MRAP) \times$

0·0136 (where RVSWI is right ventricular stroke work index in g.m.m^{-2}, MPAP is mean pulmonary artery pressure in mm Hg, MRAP is mean right atrial pressure in mm Hg, and 0·0136 is a conversion factor); LVSWI = SI × (MAP − PCP) × 0·0136, where LVSWI is left ventricular stroke work index in g.m.m^{-2}, MAP is mean arterial pressure, and PCP is pulmonary capillary pressure in mm Hg); SVR = (MAP − MRAP)/CO × 80 (where SVR is systemic vascular resistance in dyn.s.cm^{-5} and 80 is a conversion factor); PVR = (MPAP − PCP)/CO × 80 (where PVR is pulmonary vascular resistance).

VOLUME LOADING

After control measurements were made a rapid intravenous infusion of Dextran was started at a rate of 200 ml/5 min and the pulmonary capillary pressure was monitored so that it did not exceed 24 mm Hg. The total volume given to each patient varied from 200 to 1200 ml (mean 500 ml). Measurements of pressure and cardiac output were repeated only when there was a change of ⩾3 mm Hg in right atrial pressure. The change between two consecutive values of right atrial pressure was >5 mm Hg in 75% of patients and it reached a mean of 6·28 mm Hg for the group.

We used intravenous glyceryl trinitrate instead of frusemide[3] to lower the abnormally raised filling pressures. This was because the action of frusemide is not as easily controlled and may be deleterious in patients with inferior myocardial infarction complicated by shock and increased right atrial pressure[8] and because ventricular function curves can be constructed by reducing ventricular filling pressure with glyceryl trinitrate.[9] Ventricular function curves were plotted for each patient to relate ventricular filling pressure to stroke work index, stroke index, or cardiac index. We used mean right atrial pressure as the right ventricular filling pressure because it was more stable and more easily measured.[10].

STATISTICAL ANALYSIS

We used a two tailed *t* test for paired observations to compare differences between means. p values of <0·05 were regarded as statistically significant. All values are expressed as mean (1 SD).

Results

Figure 1 shows the relation between right ventricular stroke work index and mean right atrial pressure in all patients. In most the increase of mean right atrial pressure up to 10–14 mm Hg was followed by an increase in right ventricular stroke work index. But if the mean right atrial pressure exceeded 14 mm Hg right ventricular stroke work index almost always fell. Subsequent reduction of a mean right atrial pressure to <14 mm Hg by intravenous glyceryl trinitrate was followed by an increase in right ventricular stroke work index.

The mean value of optimal right atrial pressure in the group (chosen in each patient as the value of mean right atrial pressure corresponding to the maximum right ventricular stroke work index) was 11·7 (2·1) mm Hg (fig 2). The mean value of optimal pulmonary capillary pressure (chosen in each patient as the value corresponding to the maximum left ventricular stroke work index) was 16·5 (2·7) mm Hg (fig 3). In 16 patients there was a descending left

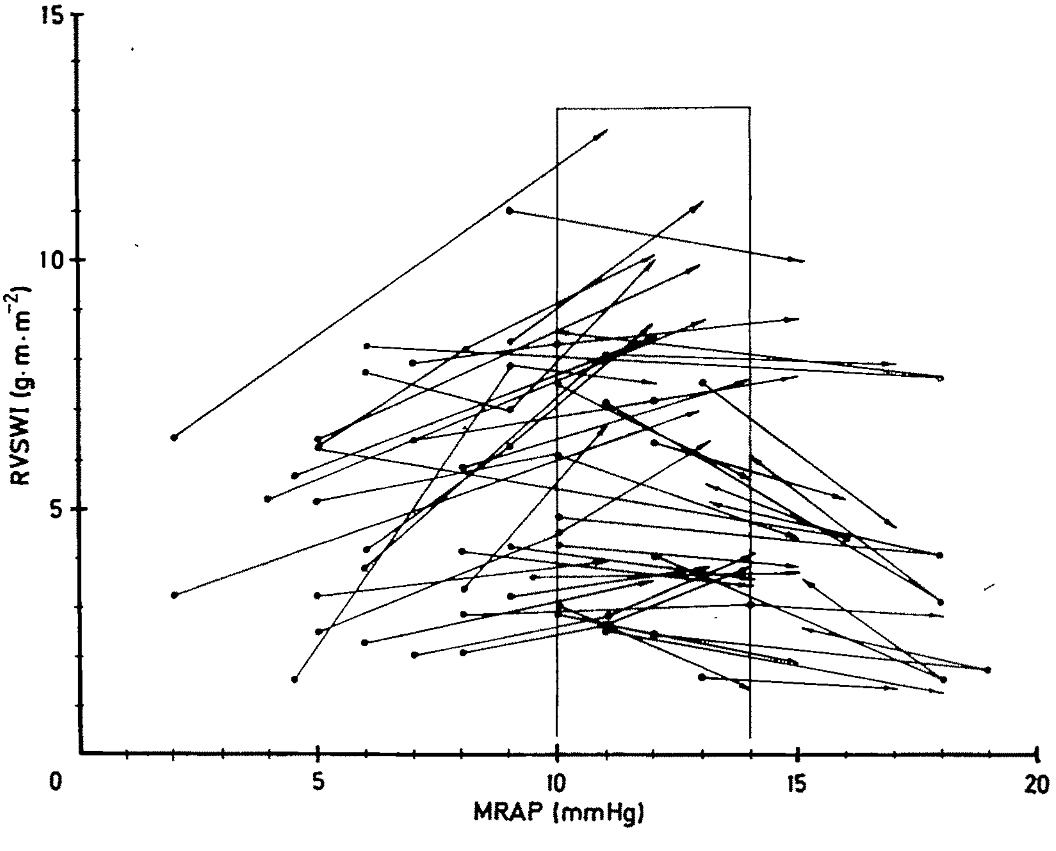

Figure 1 Relation between right ventricular stroke work index (RVSWI) and mean right atrial pressure (MRAP) in 41 patients with right ventricular infarction. The bars indicate the range of right atrial pressures at which right ventricular stroke work index is highest.

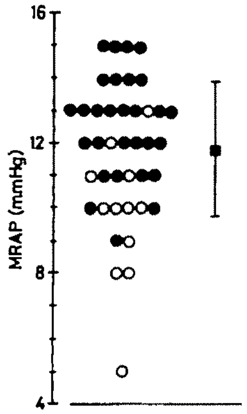

Figure 2 Optimal mean right atrial pressure (MRAP) in 41 patients with right ventricular infarction. Open circles, basal conditions; closed circles, after volume loading. Mean (1 SD) is also shown.

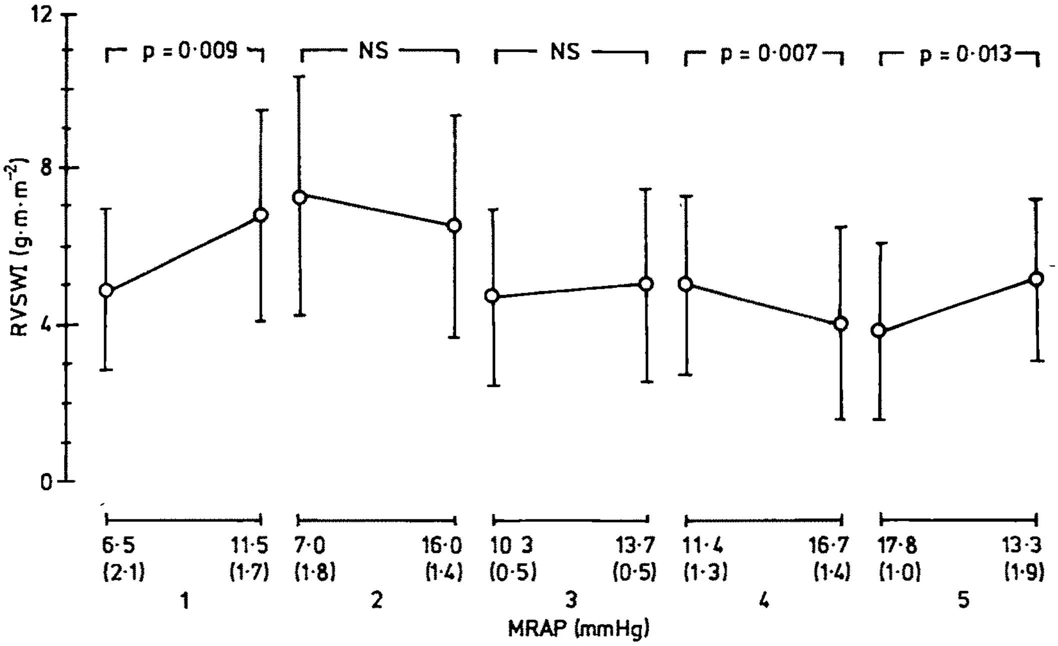

Figure 4 Right ventricular stroke work index (RVSWI) at different mean values of right atrial pressure (MRAP) for subgroups 1 to 5 See text for explanations.

ventricular function curve and an ascending right ventricular one.

To show more clearly that 10–14 mm Hg is the optimal value of right atrial pressure, we selected pairs of points representing the relation between right ventricular stroke work index (and stroke index and cardiac index) and mean right atrial pressure that corresponded to two different values of right atrial pressure obtained consecutively by dextran or glyceryl trinitrate infusion. These pairs were divided into five subgroups.

Subgroup 1 included all those pairs in which the first point corresponded to a mean right atrial pressure of < 10 mm Hg and the second point to a mean right atrial pressure ≤ 14 mm Hg.

Subgroup 2 contained all those pairs in which the first point corresponded to a mean right atrial pressure < 10 mm Hg and the second point to a mean right atrial pressure > 14 mm Hg.

Subgroup 3 included all those pairs in which both points corresponded to a mean right atrial pressure from 10–14 mm Hg.

Subgroup 4 included all those pairs in which the first point corresponded to a mean right atrial pressure ≥ 10 mm Hg and the second point to a mean right atrial pressure > 14 mm Hg.

Subgroup 5 contained all those pairs in which the first point corresponded to a mean right atrial pressure > 14 mm Hg and the second point to a lower mean right atrial pressure obtained by infusion of glyceryl trinitrate.

In subgroup 1 the increase in mean right atrial pressure from 6·5 (2·1) to 11·5 (1·7) mm Hg ($p < 0·001$) was accompanied by

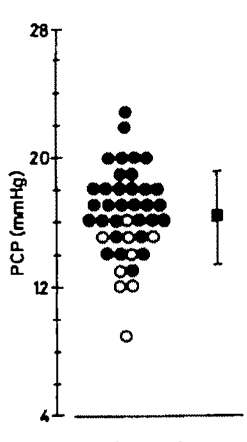

Figure 3 Optimal pulmonary capillary pressure (PCP) in 41 patients with right ventricular infarction. Open circles, basal conditions; closed circles, after volume loading. Mean (1 SD) is also shown.

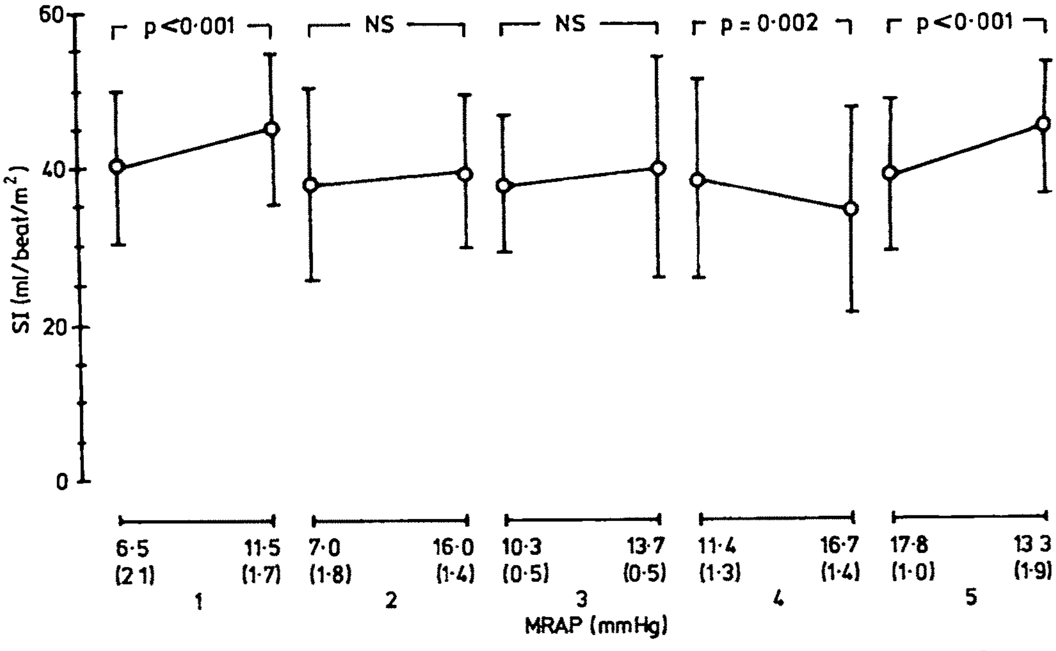

Figure 5 Stroke index (SI) at different mean values of right atrial pressure (MRAP) for subgroups 1 to 5. See text for explanations.

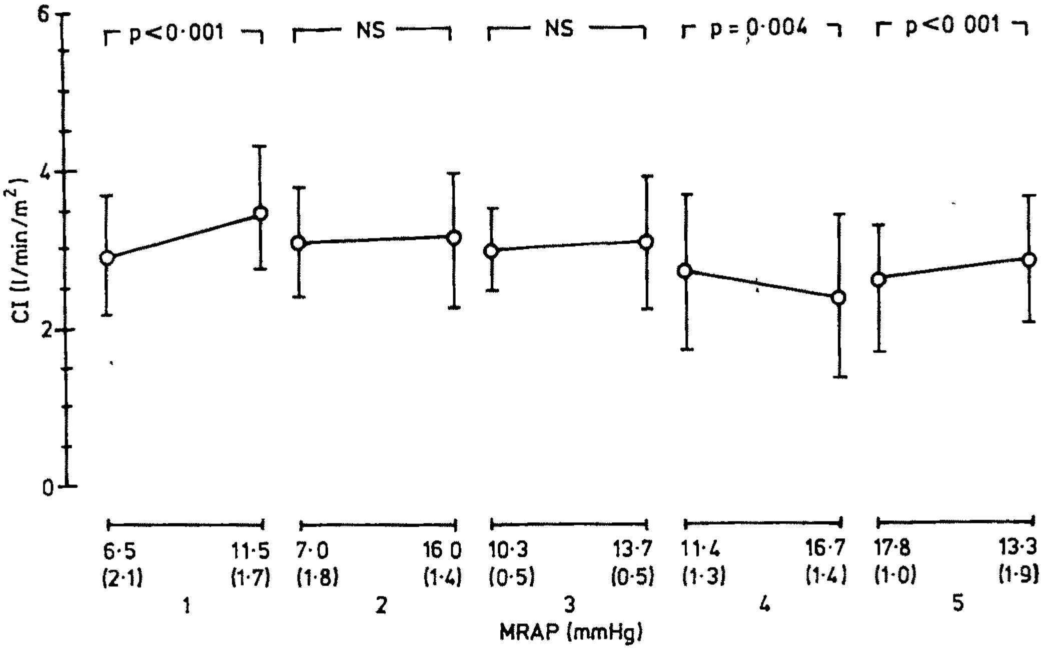

Figure 6 Cardiac index (CI) at different mean values of right atrial pressure (MRAP), for subgroups 1 to 5. See text for explanations.

a significant rise in right ventricular stroke work index from 4·9 (2·1) to 6·8 (2·7) g.m.m^{-2} ($p < 0·001$, fig 4) and in stroke index from 40·0 (9·9) to 45·2 (10·4) ml/beat/m^2 ($p < 0·001$, fig 5).

In subgroup 2 the rise of mean right atrial pressure from 7·0 (1·8) to 16·0 (1·4) mm Hg ($p = 0·009$) was followed by an insignificant change of right ventricular stroke work index from 7·3 (3·1) to 6·5 (2·9) g.m.m^{-2} (fig 4) and of stroke index from 37·9 (12·5) to 39·5 (9·8) ml/beat/m^2 (fig 5).

In subgroup 3 mean right atrial pressure increased from 10·3 (0·5) to 13·7 (0·5) mm Hg ($p < 0·001$), while neither right ventricular stroke work index (5·0 (2·5) *v* 4·7 (2·3) g.m.m^{-2}, fig 4) nor stroke index (40·1 (14·5) *v* 38·3 (8·8) ml/beat/m^2, fig 5) changed significantly.

In subgroup 4 the increase in mean right atrial pressure from 11·4 (1·3) to 16·7 (1·4) mm Hg ($p < 0·001$) was accompanied by a significant reduction of right ventricular stroke work index from 5·0 (2·3) to 4·0 (2·5) g.m.m^{-2} ($p = 0·007$, fig 4) and of stroke index from 38·4 (13·1) to 34·7 (13 5) ml/beat/m^2 ($p = 0·002$, fig 5).

In subgroup 5 the reduction in mean right atrial pressure from 17 8 (1·0) to 13·3 (1·9) mm Hg ($p = 0·002$) produced by intravenous glyceryl trinitrate was followed by a significant increase in right ventricular stroke work index from 3·8 (2·3) to 5·1 (2·1) g.m.m^{-2} ($p = 0·013$, fig 4) and in stroke index from 39·1 (9·8) to 45·0 (8·3) ml/beat/m^2 ($p < 0·001$, fig 5).

The changes in cardiac index paralleled those for stroke index (fig 6).

Discussion

The filling pressure is a major determinant of ventricular performance in intact[11-13] and diseased hearts.[1,14,15] This pressure is of critical importance in evaluating cardiac performance in patients with acute myocardial infarction.[1-3] Haemodynamic, clinical, and experimental studies[1,3,16] showed that the increase in filling pressure of the infarcted left ventricle up to the optimal level of 14–18 mm Hg in some studies[3] and of 20–25 mm Hg in others[1] was followed by a parallel rise in cardiac output, stroke index, and left ventricular stroke work index. But data about the optimal filling pressure of the right ventricle in patients with right ventricular infarction are few and inconclusive.[3,4]

Some regarded as optimal mean right atrial pressures of 6–8 mm Hg,[3] but in their patients the real incidence of right ventricular infarction was unknown. For others the optimal value was 15·6 mm Hg,[4] but only in a subgroup of patients with cardiac index of <2·2 l/min/m^2. The range of haemodynamic function in patients with right ventricular infarction is much wider.

When we plotted ventricular function curves for right ventricular stroke work index (as a more specific indicator of the function of this ventricle) against mean right atrial pressure (fig 1) we found that an increase of mean right atrial pressure up to 10–14 mm Hg was almost always followed by a rise in right ventricular stroke work index, whereas increases in mean right atrial pressure to above these values resulted in a level or even descending line. When mean right atrial pressure returned to 10–14 mm Hg after treatment with glyceryl trinitrate right ventricular stroke work generally increased. The mean value of optimal right atrial pressure of the group, selected in each patient as the value of mean right atrial pressure corresponding to the highest right ventricular stroke work index, was found to be 11·7 (2·1) mm Hg (fig 2). This finding was supported by the analysis of pairs of points representing the relation between right ventricular stroke work index (and stroke index and cardiac index) and mean right atrial pressure that corresponded with the two different values of right atrial pressure produced by infusions of dextran or glyceryl trinitrate (figs 4–6). This analysis showed that the right ventricular stroke work index increased only in subgroups 1 and 5. In subgroup 1, the rise of mean right atrial pressure from 6·5 (2·1) to 11 5 (1·7) mm Hg was followed by a considerable increase in right ventricular stroke work index and stroke index. In subgroup 5, too, right ventricular stroke work index and stroke index increased significantly when mean right atrial pressure was reduced from 17·8 (1·0) to 13·3 (1·9) mm Hg by infusion of glyceryl trinitrate.

The improvement in right ventricular performance at optimal filling pressure is a result of the stretching to their optimal length of the myocardial fibres that have survived necrosis; this, according to Starling's law, increases their contraction.

In subgroup 4, an increase in mean right atrial pressure from 11·4 (1·3) to 16·7 (1·4) mm Hg led to a significant decrease in the performance of the right ventricle. Others, too, have reported no improvement in right ventricular performance in patients with predominant right ventricular infarction when right atrial pressure is abnormally raised.[17] The increase of right ventricular filling pressure above the optimal values reduces right ventricular performance because it augments the wall stress and the rigidity of the thin-walled right ventricle and affects left ventricular geometry[18–20] and interventricular septal motion.[19 21 22] For these changes that derive from ventricular interdependence the intact pericardium will also have constrictive effects on the dilated heart.[23–25]

We found that the optimal pulmonary capillary pressure was 16·8 (2·7) mm Hg (fig 3), nearly the same as that found in patients with left ventricular infarction.[3] In 16 patients, however, the left ventricular function curves took the opposite course to those of the right ventricle. Others too have described patients in shock owing to right ventricular infarction who showed values of left ventricular filling pressure within optimal limits.[26] These data clearly indicate that to maintain adequate cardiac performance in patients with biventricular infarction, both the left and right ventricular filling pressures need to be optimal.

Our study showed that the control of right ventricular filling pressure in patients with biventricular infarction enables the regulation to some degree of right ventricular performance according to Starling's law. Cardiac and stroke index increased and the right ventricle reached its maximum stroke work index when the filling pressure was 10–14 mm Hg. These values could, therefore, be considered as the optimal value of right ventricular filling pressure in patients with right ventricular infarction, though there were individual variations.

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Ambulatory pulmonary arterial pressure in primary pulmonary hypertension: variability, relation to systemic arterial pressure, and plasma catecholamines

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Abstract

The variability of pulmonary arterial pressure, the relation of pulmonary pressure to systemic pressure, pulmonary pressure responses to stimuli (exercise, hypoxia, smoking, free ambulation), and plasma catecholamine responses were assessed in five patients with primary pulmonary hypertension. Ambulatory monitoring techniques provided data for the computerised analysis of continuous, beat-to-beat, direct recordings of both pulmonary and systemic arterial pressures for 8 to 10 hours. The absolute variability of pulmonary arterial pressure and the magnitude of absolute changes in this variable in response to stimuli were increased in primary pulmonary hypertension. The variability of systemic pressure was similar to that in healthy volunteers. Basal and stimulated plasma catecholamine values were normal, suggesting preservation of normal sympathetic nervous system activity in primary pulmonary hypertension.

Primary pulmonary hypertension is a rare disease[1] and its cardinal characteristic, an increase in pulmonary arterial pressure, is difficult to measure without catheterisation of the pulmonary artery. For these reasons data on levels and variability of pulmonary artery pressure in primary pulmonary hypertension are scant and confined to intermittent readings in restricted, catheterised patients.[2,3] Spontaneous variability in pulmonary pressure has been put forward as a major impediment to the assessment of responses in therapeutic trials of vasodilator agents in primary pulmonary hypertension. However, our knowledge of the magnitude of such variation is very limited.[2,3] Further, in these patients, the behaviour of the pulmonary circulation during unrestricted ambulation and how responses to physiological stimuli may differ from normal are quite unknown. It is also not known whether the relation between concomitant shifts in systemic and pulmonary arterial pressures is distorted in primary pulmonary hypertension. Finally, the activity of the sympathetic nervous system in primary pulmonary hypertension is largely unexplored. We have previously reported a technique which allows the continuous recording of pulmonary artery pressure in unrestricted people over prolonged periods[4] and described the range and variability of pulmonary artery pressure and its relations to systemic arterial pressure and plasma catecholamines in healthy volunteers during several everyday activities.[5] The current report is the first to describe alterations in these variables at rest and in response to exercise, eating, smoking, and hypoxia in ambulant patients with primary pulmonary hypertension and it compares these findings with those reported in earlier studies of healthy volunteers.

Patients and methods

The protocol was approved by the hospital ethics committee and all patients gave informed consent. The study group consisted of five patients (four women and one man, aged 24 to 60 years (mean 41 years)) with primary pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg at rest, no secondary cause identified by full evaluation[6]). We compared the results with those in six healthy people (three women, three men) aged 24 to 40 years (mean 29 years) who were studied earlier.[5] Three patients were treated with captopril (25 mg twice or three times a day) and two were untreated.

The patients were studied on day 4 of a diet containing a constant amount of sodium (80 mmol/day) and potassium (60 mmol/day) and no caffeine. Between 0800 and 1000 hours on the study day they underwent pulmonary artery catheterisation via an antecubital vein with a fluid filled F5 Goodale-Lubin catheter. The catheter was connected to a portable transducer-perfusion unit as already described.[4] After careful clinical assessment of arterial blood supply to the left arm, the left brachial artery was cannulated with a F3 Seldicath connected to a second portable transducer-perfusion unit. The left radial pulse and circulation in the left hand were checked throughout the study. Signals from the two transducers, together with the electrocardiogram from chest leads, were continuously recorded on separate channels of a Medilog miniaturised, multichannel tape recorder worn on a belt at the waist. The pulmonary arterial pressure signal was processed by an AM4 recorder module set for linear amplification of pressures between 0 and 150 mm Hg. The frequency response for both systemic and pulmonary artery pressure was linear to 8 HZ.[4] The methods of continuous ambulatory recording of both pulmonary and systemic arterial pressures have been described elsewhere.[4 5 7] To eliminate zero shift problems caused by postural changes with the low pressure pulmonary system the transducers were worn on the anterior chest wall directly over the tip of the catheter in the main pulmonary artery (placed under fluoroscopic guidance) and the patients remained upright, either seated or standing, throughout the recording period. Both transducers were calibrated with a mercury column at the beginning and at the end of each study and also at approximately the midpoint of the protocol.

After catheterisation, patients were given breakfast and allowed a period of 1·5 hours to become accustomed to their portable equipment. Each participant then progressed through a sequence of interventions. These were spaced at least an hour apart, and between interventions patients were able to move about, talk, sit, read, sleep, stand, and visit the toilet while recordings continued. Careful note of body posture and activity was made throughout by one observer who used a stopwatch and diary. As a safety measure, an additional member of the research medical staff was present at all times.

Exercise was performed on a stationary upright bicycle with a graded submaximal exercise test (modified Naughton protocol[8]) to 75% of maximum predicted heart rate. Blood was sampled for plasma catecholamine concentrations 10 minutes before exercise (− 10 minutes) and when exercise started (0 minutes) and at the peak exercise as well as 15, 20, 30, and 60 minutes after the end of exercise.

Hypoxia—The patients breathed a gas mixture of 10% oxygen in nitrogen for 30 minutes, or as long as it was tolerated, while in the sitting position. During this intervention, arterial samples for blood gas analysis together with venous blood for catecholamines were drawn at − 10 minutes, 0 minutes, peak hypoxia, and 30 minutes after return to breathing room air.

Smoking—Three patients (smokers) smoked two commercial filter tipped cigarettes (5·5 cm of each) in 10 minutes. Venous plasma catecholamine samples were taken at 0 and 10 minutes.

Eating—Patients ingested a 2·5 MJ (man) or 2·0 MJ (women) lunch over a period of 15 minutes.

Venous samples were collected into chilled tubes, centrifuged at 4°C, and stored at − 80°C before radioenzymatic assay for plasma catecholamines.[9]

For data analysis, a PDP-11 computer was programmed to calculate average systolic, mean, and diastolic pulmonary and systemic pressures and heart rate for successive groups of 10 heartbearts. These results were used to provide graphical and digital printouts with means and standard deviations for periods of interest. Mean values of pressures and heart rate were calculated for each of the 16–20 half hour periods of total recording time. The short term variability of these variables was assessed by the method of Mancia *et al*[10] in which the standard deviations and coefficients of variation were calculated for each separate half hour period. An index of longer term variability was provided by the standard deviation and variation coefficient derived from averaging the 16–20 mean half hourly values. Two way analysis of variance with repeated measures and the *t* test for paired data were used to test for significant changes in pressure and heart rate and hormone concentrations during interventions. Successive 1 minute mean values of pulmonary and systemic pressures were correlated (product-moment correlation coefficient) during the periods of interest. To compare resting and intervention related plasma concentrations of catecholamines, systemic and pulmonary arterial pressures, heart rate, and the variability of the haemodynamic indices in patients and healthy volunteers studied earlier we used the non-parametric Mann-Whitney test.[11] Intergroup comparisons were also made by analysis of variance (BMDP program P2V) with "group" (normal or pulmonary hypertensive) and "time" as repeated measures. Interactions between "group" and "time" were inspected to allow detection of significant non-parallelism between groups in the response of pressures to any given stimulus. Data are given as mean (SEM) unless stated otherwise.

Results

Studies were completed without complications. On day 3 of the constant diet 24 hour urinary excretion of sodium was 69 (5) mmol.

For the 8–10 hour period of continuous recording, mean values for pulmonary and systemic pressures (n = 5) were 49·2 (8·2)/23·0 (4·8) and 115·4 (4·7)/65·2 (24) mm Hg respectively. Pulmonary, but not systemic, pressures were significantly greater than the corresponding values in our earlier study of healthy volunteers (15·7/6·3 mm Hg ($p < 0·01$) and 121·1/72·4 mm Hg (NS) respectively (fig 1). Pulmonary pressure showed similar variability within half hour periods as between half hour periods and in both cases absolute variations (mm Hg) but not percentage coefficients of variation significantly exceeded values in healthy volunteers (table 1). Over 8–10 hours the variation in systolic pulmonary arterial pressure in individual patients at rest (that is seated, unstimulated, and a minimum of 5 minutes clear of any activity or intervention) was 20–32 mmHg (mean 23·2 (2·2) mm Hg). Pulmonary diastolic pressures at rest varied by 8–15 mm Hg (mean 12·2 (1·9) mm Hg). Corresponding values for the mean range covered by resting pulmonary pressures in our volunteer group were significantly lower (12·1 (1·2) and 6·8 (1·3) mm Hg for systolic and diastolic pressures respectively) ($p < 0·01$ for both comparisons). Swings in resting pulmonary pressure lasted several minutes and occurred gradually, and no precipitous changes (that is occurring within seconds) were recorded at rest. Changes in resting pulmonary pressure bore no clear relation to time of

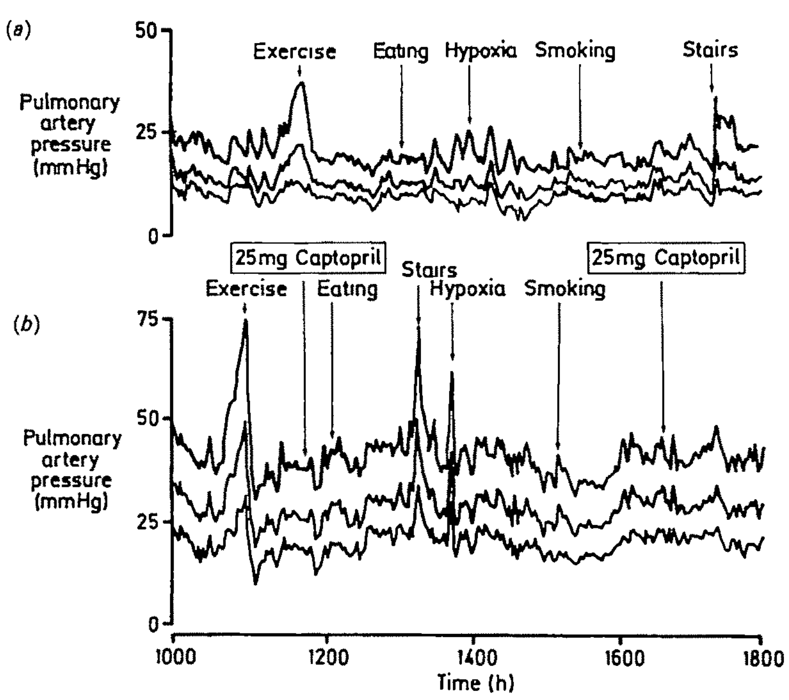

Figure 1 Continuous recordings of pulmonary systolic, mean, and diastolic pressures plotted from serial integrated one minute mean values over 8 hours and during several activities and interventions. (a) Data from a healthy volunteer and (b) a patient with primary pulmonary hypertension (both aged 28 years).

captopril dose (and were similar in both treated and untreated patients) or any other easily discernible external stimulus. Coefficients of variation (SD mean %) for entire recordings in these patients for pulmonary systolic and diastolic pressures were 15·1 and 20·9% respectively, within half hours (table 1), an index of short term fluctuation. Coefficients from data entirely confined to recordings taken in seated, resting patients (at least 100 minutes of recording per patient derived from integrated one minute mean values) were 10·6% and 15·2% for pulmonary systolic and diastolic values respectively.

The variability of both systemic arterial pressure and heart rate did not significantly differ from normal (table 1). Table 2 gives pressures and heart rates averaged for the total recording period and for separate interventions.

Inspection of computer graph printouts generally showed that pulmonary pressure, systemic pressure, and heart rate moved in parallel (figs 2 and 4)—except during hypoxia when pulmonary pressure clearly rose in the absence of a significant change in systemic pressure (fig 3). Overall, for serial 30 minute integrated values, there was a positive correlation between mean pulmonary and systemic pressures in three patients (r values 0·58, 0·68, 0·72; $p < 0·01$ to $p < 0·001$), but this correlation was not found in two patients (r = 0·12, 0·22 (NS)). This variable relation between systemic and pulmonary pressures contrasted with findings in healthy volunteers for whom uniformly strong, positive correlations were found.

Visual comparison of graphic outputs of pulmonary pressures for the entire period of recording from healthy volunteers and patients with primary pulmonary hypertension indicated that the direction of response of pulmonary pressures to any given stimulus was similar in both groups, but the group with pulmonary hypertension showed a more abrupt and greater absolute change (from a higher baseline value) (fig 1). This impression was confirmed by detailed analysis of pressure responses during standardised interventions.

EXERCISE

The duration of exercise required for patients to achieve 75% of predicted maximum heart rate varied from 13 to 20 minutes (mean 16·6 (2·7)) and tended to be shorter than in healthy volunteers (21·2 (3·3) minutes, difference NS). Pressures in both pulmonary and systemic circuits increased abruptly at first and then continued a more gradual climb until exercise was halted ($p < 0·001$ for changes from resting values in both pulmonary and systemic pressures and systolic and diastolic pressures (fig 2). Throughout exercise pulmonary, but not systemic, pressures were significantly greater than in the healthy volunteers ($p < 0·001$, $p < 0·01$ for systolic and diastolic values respectively, table 2) and group-time interaction analysis showed a significantly steeper rise in pulmonary pressures but not systemic pressures with time in the patient group ($p < 0·001$ for both pulmonary systolic and diastolic pressures). Pulmonary systolic pressures rose by 43 mm Hg from rest to peak exercise compared with only 19 mm Hg in healthy volunteers. Pulse pressures increased in both circuits in

Table 1 Pulmonary and systemic arterial pressures for recording over 8–10 hours

			Variability			
			Within 0·5 h periods		*Between 0·5 h periods*	
		Mean (SEM) (mm Hg)	*SD (mm Hg)*	*CV (%)*	*SD (mm Hg)*	*CV (%)*
PAP						
Systolic	1°PHT	49·2 (8·2)**	7·2**	15·1	7·5*	15·3
	Normal	15·7 (1·0)	3·8	25·8	3·5	22·0
Diastolic	1°PHT	23·0 (4·8)*	3·7**	20·9	3·8*	19·5
	Normal	6·3 (0·7)	2·4	42·7	1·8	31·1
SAP						
Systolic	1°PHT	115·4 (4·7)	9·3	8·1	8·5	7·4
	Normal	121·1 (5·3)	8·1	6·8	9·3	8·0
Diastolic	1°PHT	65·2 (2·4)	7·0	10·8	4·4	6·8
	Normal	72·4 (3·8)	6·0	8·7	6·0	8·3
Heart rate (bpm)	1°PHT	89·8 (6·3)	6·0	6·4	6·8	6·8
	Normal	91·0 (2·9)	9·3	10·1	11·3	11·3

1°PHT, primary pulmonary hypertension, PAP, pulmonary artery pressure; SAP, systemic arterial pressure, CV, coefficient of variation (SD/mean %)—n = 5 for 1°PHT and n = 6 for healthy volunteers
Significance of difference compared with normal: *$p < 0·05$, **$p < 0·01$

Table 2 Pulmonary and systemic arterial pressures and heart rate during total recording and interventions (mean (SEM))

	Pulmonary arterial pressure		Systemic arterial pressure		
	Systolic (mm Hg)	*Diastolic (mm Hg)*	*Systolic (mm Hg)*	*Diastolic (mm Hg)*	*Heart rate (beats/min)*
Total recording:					
1°PHT (n = 5)	49·2 (8·3)	23·2 (4·4)	116·1 (4·8)	65·3 (2·7)	92·3 (4·5)
Normal (n = 6)	15·7 (1·0)	6·3 (0·7)	121·1 (5·3)	72·4 (3·8)	91·0 (2·9)
Resting.					
1°PHT (n = 5)	47·1 (6·7)	22·2 (4·2)	114·6 (6·9)	63·4 (3·2)	91·4 (4·1)
Normal (n = 6)	13·9 (1·1)	5·5 (0·9)	118·7 (4·9)	69·0 (2·7)	84·8 (3·4)
Exercise.					
1°PHT (n = 5)	89·6 (14·3)***	37·2 (6·9)***	166·2 (14·3)	80·8 (4·6)	125·4 (9·4)
Normal (n = 6)	33·3 (1·7)	12·0 (0·9)***	157·0 (7·3)	85·8 (4·2)	152·0 (5·4)***
Eating:					
1°PHT (n = 5)	53·8 (8·1)	25·4 (4·5)	124·0 (8·2)	67·6 (5·1)	94·2 (7·5)
Normal (n = 6)	16·0 (1·9)	7·2 (1·6)	129·8 (6·7)*	79·0 (3·7)*	95·5 (4·2)
Hypoxia:					
1°PHT (n = 5)	67·2 (9·6)**	30·2 (4·8)*	114·6 (6·4)	58·8 (4·5)	96·6 (8·3)**
Normal (n = 6)	25·0 (3·8)***	10·0 (1·4)	102·8 (11·0)*	56·8 (9·2)*	105·3 (3·5)
Smoking:					
1°PHT (n = 3)	48·3 (14·3)	21·7 (7·6)	136·0 (3·5)**	71·3 (3·9)	99·7 (14·3)
Normal (n = 6)	15·8 (1·6)	6·4 (0·8)	125·8 (6·7)**	78·4 (5·6)	105·0 (2·8)***

1°PHT, data from patients with primary pulmonary hypertension, Normal, healthy volunteers.
Significance of change from resting values before interventions. * $p < 0·05$, ** $p < 0·01$, *** $p < 0·001$.
At all times pulmonary systolic and diastolic pressures were, as expected, significantly greater in 1°PHT patients than in healthy volunteers ($p = < 0·005 - p < 0·001$). Systemic diastolic pressures differed between groups for "eating" only ($p < 0·001$). Systemic systolic pressures did not differ significantly between groups at any time.
Values given are for peak exercise, peak hypoxia (taken at 80% duration of intervention), 8 minutes of eating, and 5 minutes of smoking and are averaged over a mean time of 100 minutes for "resting".

both groups ($p < 0·001$ for change from baseline for all pressures). Successive corresponding one minute mean values of pulmonary and systemic pressures during exercise were closely correlated in all patients (range of r values 0·88–0·97, $p < 0·001$ for all). Plasma catecholamine concentrations rose normally with exercise (table 3) and peak values for noradrenaline (6·27 (0·24) nmol/l and adrenaline (889·65 (218·32) pmol/l) did not differ significantly from those achieved in our healthy volunteers (6·65 (1·03) nmol/l and 622·21 (169·20) pmol/l respectively).

HYPOXIA

Patients tolerated exposure to 10% oxygen in nitrogen for 4–20 minutes compared with healthy volunteers who tolerated 10% oxygen for 8–30 minutes. Systemic pressure did not alter significantly from resting values (fig 3, table 2). Arterial oxygen saturation fell significantly (95·0 (1·4) to 74·1 (5·5)%; $p < 0·001$) by the end of the hypoxic period. Pulmonary pressure rose in all patients ($p < 0·01$ and $p < 0·05$ for systolic and diastolic values respectively, fig 3). Heart rate rose significantly (fig 3, table 2). Absolute increases in pulmonary pressure in the patients were significantly greater than in healthy volunteers ($p < 0·001$ and $p < 0·01$ for systolic and diastolic values respectively, table 2). However, time-group interaction analysis indicated parallel behaviour of pulmonary arterial pressure in both groups. Plasma noradrenaline was unchanged while adrenaline values rose significantly (table 3), similar to the response seen in healthy volunteers.

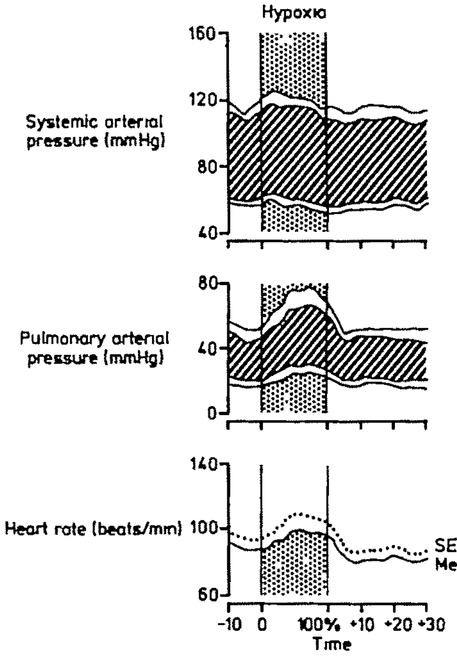

Figure 3 Changes in pulmonary and systemic arterial pressures and heart rate (mean (SEM)) with acute hypoxia in five patients with pulmonary hypertension. See fig 2 for symbols and calculation of plotted values. Duration of hypoxia varied between patients and is shown as 0–100% on the horizontal axis.

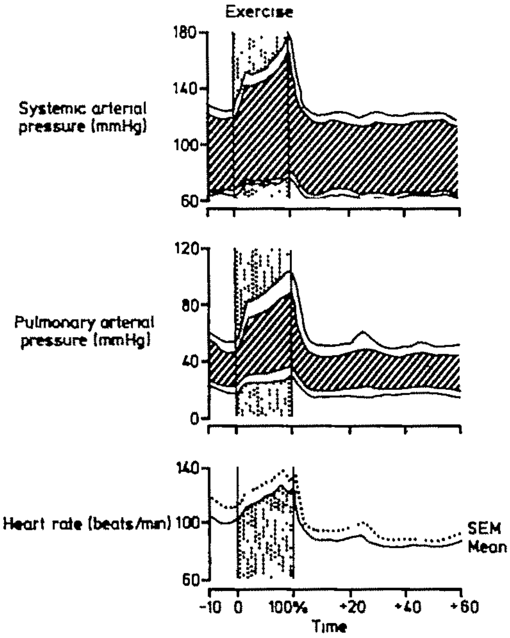

Figure 2 Changes in pulmonary and systemic arterial pressures and heart rate (mean (SEM)) with exercise in five patients with pulmonary hypertension. Standard errors were calculated for integrated mean pressures and heart rate from successive one minute intervals before, during, and after exercise. Exercise time varied between patients (shown as 0–100% on horizontal axis) and standard errors were calculated in 10% steps for duration of exercise (shown as continuous lines above mean systolic and below mean diastolic pressures, and a dotted line above mean heart rate).

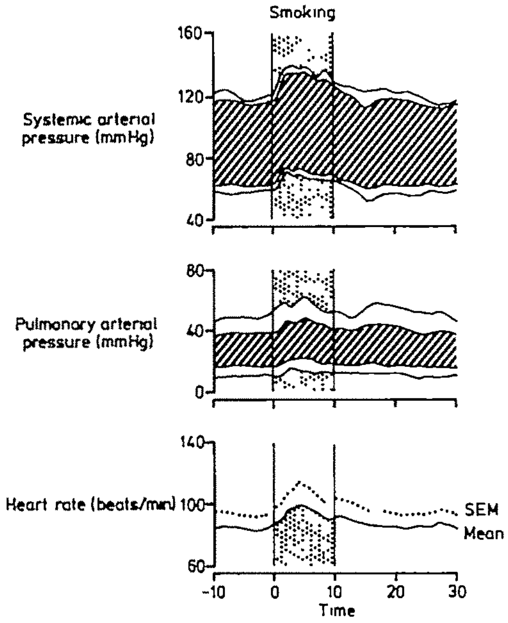

Figure 4 Changes in pulmonary and systemic arterial pressures and heart rate (mean (SEM)) when two cigarettes were smoked, between 0–10 min, by three patients with pulmonary hypertension. See fig 2 for variables, symbols, and calculation of plotted values.

SMOKING

Three patients (smokers) smoked two standard cigarettes in 10 minutes. During smoking systemic pressure rose significantly above resting values and returned to baseline within five minutes of the patients finishing the cigarettes (fig 4). The tendency for pulmonary pressure and heart rate to increase was not statistically significant. These variables showed no discernible response in normal subjects. Patients retained a strong, positive correlation between pulmonary and systemic pressures throughout smoking (range of r values, $r = 0{\cdot}69–0{\cdot}88$, $p < 0{\cdot}01$ to $p < 0{\cdot}001$). In all three patients both noradrenaline and adrenaline concentrations rose (table 3).

EATING

The tendency for the systemic and pulmonary pressures and heart rate to increase during eating did not achieve statistical significance (table 2). The overall pattern of haemodynamic responses was similar to that seen in healthy volunteers (table 2). Time-group interaction analysis showed no difference between the two groups.

MISCELLANEOUS

Quiet walking was associated with modest increases and stair-climbing with sharp increases in pulmonary pressure above resting values. Two patients slept for brief periods while sitting and all pressures and heart rates were notably lower at these times. An incidental observation was the lack of any cardiac arrhythmia beyond occasional supraventricular and ventricular extrasystolic beats during recordings.

Discussion

Knowledge of the fluctuations in pulmonary arterial pressure in health and disease is critical for interpretation of data obtained during catheterisation of patients with primary pulmonary hypertension. We used techniques enabling the computerised integration of continuous, beat to beat, direct recording of both pulmonary and systemic arterial pressure to acquire such data in patients with primary pulmonary hypertension during rest, free ambulation, and various interventions. Carefully standardised conditions of study allowed us to compare our findings with those in a group of healthy volunteers studied earlier.[5]

Over periods of 8–10 hours and in the course of several interventions and activities pulmonary pressure was maintained above normal values in these patients (fig 1, table 2). Absolute variation in pulmonary pressure was greater in primary pulmonary hypertension than in the healthy volunteers (table 1). Relative variation (coefficients of variation) were similar or less than in the volunteers (table 1) and somewhat greater than the 8% figure calculated by Rich *et al* for mean pulmonary pressure from intermittent readings in resting, supine patients.[5] These data show the increased absolute, but not proportional, variability of pulmonary pressure in primary pulmonary hypertension. We have also confirmed earlier reports of sig-

Table 3 Plasma catecholamines (mean (SEM))

	Time (min)						
Exercise:	*−10*	*0*	*Peak*	*+15*	*+20*	*+30*	*+60*
Noradrenaline (nmol/l)							
1°PHT (n = 4)	2·2 (0·3)	2·5 (0·4)	** 6·3 (2·0)	2·1 (0·4)	2·0 (0·1)	2·2 (0·2)	2·5 (0·5)
Normal (n = 6)	3·7 (0·5)	4·4 (0·5)	** 6·6 (1·0)	3·2 (0·2)	3·1 (0·2)	3·0 (0·3)	3·0 (0·3)
Adrenaline (pmol/l)							
1°PHT (n = 4)	431 (109)	497 (65)	** 890 (218)	551 (76)	448 (49)	480 (82)	508 (87)
Normal (n = 6)	420 (71)	442 (87)	* 622 (169)	556 (130)	426 (136)	442 (98)	239 (87)
Hypoxia:	*−10*	*0*	*Peak*	*+30*			
Noradrenaline (nmol/l)							
1°PHT (n = 4)	2·4 (0·3)	2·5 (0·3)	2·7 (0·5)	2·0 (0·1)			
Normal (n = 6)	5·3 (0·6)	4·0 (0·4)	4·2 (0·5)	3·1 (0·4)			
Adrenaline (pmol/l)							
1°PHT (n = 4)	519 (82)	862 (1 80)	*1173 (371)	508 (109)			
Normal (n = 6)	535 (175)	437 (115)	* 933 (213)	486 (65)			
Smoking.		*0*	*Peak*				
Noradrenaline (nmol/l)							
1°PHT(n = 3)		1·9 (0·2)	3·0 (0·1)				
Normal (n = 6)		3·5 (0·5)	4·0 (0·3)				
Adrenaline (pmol/l)							
1°PHT (n = 3)		295 (126)	851 (295)				
Normal (n = 6)		338 (71)	720 (164)				

Within groups two way analysis of variance of all time points followed by paired *t* test comparing 0 and peak values indicated a significant rise in both catecholamines with exercise, and in adrenaline alone during hypoxia for both groups.
*$p < 0{\cdot}05$, **$p < 0{\cdot}01$, ***$p < 0{\cdot}001$.

nificant spontaneous fluctuations in pulmonary pressure in primary pulmonary hypertension apparently unrelated to medication or any other easily discerned stimulus.[2 3]

To our knowledge, variability in systemic pressure and the relation of systemic to pulmonary pressures have not previously been reported in primary pulmonary hypertension. Our data indicate that the values of variability in systemic pressure in our patients with primary pulmonary hypertension resembled those seen in healthy volunteers. These data imply that the lesion resulting in the high values of (and excessive absolute variation in) pulmonary pressures seen in this patient group exerts no similar effect on fluctuations in systemic pressure.

Changes in pulmonary pressures during exercise were directionally similar but of greater absolute magnitude than those seen in healthy volunteers. Hypoxia also resulted in a greater rise in pulmonary pressure than was seen in healthy volunteers.[5 12] Over the whole study period we found generally parallel movement of pulmonary and systemic pressures in three patients, but no relation in two patients. In contrast, pulmonary and systemic pressures changed in parallel in all healthy volunteers. Although no clinical characteristics predicted the absence of this relation in the two patients, it may be related to the abnormal pulmonary vasculature.

The activity of the sympathetic nervous system has not previously been assessed in primary pulmonary hypertension. We continuously monitored heart rate and took frequent samples to estimate plasma concentrations of catecholamine at rest and during interventions. Despite the higher mean age of patients their baseline concentrations of plasma catecholamines tended to be lower than in the healthy volunteers and the peak values attained with interventions were similar in the volunteers and those with pulmonary hypertension. The pattern of change in plasma catecholamines with interventions was similar in both groups. Care must be taken in extrapolating from plasma catecholamine concentrations to sympathetic nervous activity and little can be divined concerning sympathetic traffic to any single organ.[13] Nevertheless, our data suggest that primary pulmonary hypertension is not attended by any gross alteration in either basal or stimulated global sympathetic nervous system activity.

Resting heart rates were similar in the two groups (table 2). However, it is noteworthy that during exercise, patients with primary pulmonary hypertension achieved slightly greater systemic pressures, and far greater pulmonary pressures than normal in association with substantially lower heart rates (table 2). Variability in heart rate also tended to be lower in the patient group (table 1). The groups were not well matched for age and the apparent diminished responsiveness in heart rate may simply reflect the greater age of the patients. An alternative explanation is that vagal inhibition of heart rate was enhanced as a result of increased stimulation of baroceptors in the pulmonary arteries or right ventricle[14] in primary pulmonary hypertension. Further studies with age and weight matched controls, together with assessment of the effect of atropine, may clarify this issue.

In summary, our data indicate that the absolute variability of pulmonary arterial pressure and the magnitude of absolute changes in pulmonary arterial pressure in response to stimuli are enhanced in primary pulmonary hypertension. The variability of systemic arterial pressure is normal. Short term congruency of shifts in pulmonary and systemic pressures are preserved but in some patients the relation between systemic and pulmonary pressures, over periods of hours, is weakened. Basal and stimulated plasma catecholamine values are normal, suggesting preservation of normal sympathetic nervous system activity in primary pulmonary hypertension.

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Enhanced morphological diagnosis in infective endocarditis by transoesophageal echocardiography

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Abstract

Thirty three consecutive patients with clinically suspected endocarditis were studied by both precordial cross sectional echocardiography and transoesophageal echocardiography. The diagnostic value of both techniques was assessed. The data were compared with findings at operation in 25 patients. In 21 patients with native valve endocarditis precordial echocardiography showed evidence of vegetations in six patients and suggested their presence in nine. Transoesophageal echocardiography identified vegetations in 18 patients. Complications were seen in four patients at precordial echocardiography and in nine patients at transoesophageal echocardiography. Precordial echocardiography did not show vegetations in any of the 12 patients with prosthetic valve endocarditis whereas transoesophageal echocardiography showed vegetations in four. Complications were seen in four patients at precordial echocardiography and in 10 at transoesophageal echocardiography. Echocardiographic findings were confirmed at operation in all 25 operated patients. In two patients both echocardiographic techniques had missed the perforation of the cusps of the aortic valve that was seen at operation, but this had no effect on patient management. Transoesophageal echocardiography is the best diagnostic approach when infective endocarditis is suspected in patients with either native or prosthetic valves.

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Before the introduction of transoesophageal echocardiography, high resolution precordial cross sectional echocardiography was widely accepted as a valuable method of diagnosing infective endocarditis. But this method has limitations, and false positive[1-3] as well as false negative diagnoses have been reported in patients who eventually required operation.[4-6] In patients with a prosthetic valve precordial echocardiography is hampered because the prosthesis interferes with the ultrasound beam.[7-9] Cardiac catheterisation is of limited value in such patients.[6 10] The introduction of transoesophageal echocardiography provided an alternative diagnostic approach.[11-13]

We assessed the diagnostic value of transoesophageal echocardiography in identifying abnormalities caused by infective endocarditis. The results were compared with the findings at precordial echocardiography and at operation.

Patients and methods

STUDY GROUP

Over a 4 year period (1984–1988) 33 consecutive patients (24 men and nine women; mean age 45, range 18–81) with clinically suspected infective endocarditis were investigated by precordial echocardiography and subsequently by transoesophageal echocardiography (the interval between studies was <3 days).

The clinical diagnosis of infective endocarditis was supported by bacteriological findings (32 patients had positive blood cultures) and surgical description (25 patients). Indications for cardiac surgery were: congestive cardiac failure (15 patients); persistent fever (five patients); multiple embolism (one patient); and endocarditis during the waiting period for elective cardiac surgery in our unit (four patients).

Twenty one patients had endocarditis of a native valve (12 mitral and nine aortic). The underlying valve disease was mitral stenosis in two, mitral valve myxomatous degeneration in three, and bicuspid aortic valve in four patients (tables 1 and 2). Operation was performed within 16 days at the transoesophageal echocardiographic study in 15 patients (range 1–16 days). The six unoperated patients were successfully treated with antibiotics.

Twelve patients were referred with prosthetic valve endocarditis. The prostheses implanted included two mitral; six aortic, mitral and aortic in one; and mitral, aortic, and tricuspid in three (table 3). Operation was performed in 10 patients within seven days of the transoesophageal echocardiographic study (range 1–7 days). One patient died and necropsy was not performed. One patient was treated successfully with antibiotics.

EQUIPMENT AND TECHNIQUES

We performed precordial cross sectional echocardiographic studies with a Toshiba SSH-65A, Toshiba SH 160, or Hewlett-Packard HP 77020 AC imaging system. The frequency of the transducers used was 3·5, 3·75, or 5 MHz respectively.

The transoesophageal study was performed with a 5·6 MHz phased array transducer mounted at the tip of a gastroscope tube. The

Table 1 Detection of vegetations or complications or both in patients with mitral valve endocarditis

Native mitral valve	Precordial echocardiography		Transoesophageal echocardiography		
Patient no	Vegetations	Complications	Vegetations	Complications	Operation
1	–	–	+	–	NP
2	–	–	–	MV cordal rupture	P
3	?	–	–	MV cordal rupture	P
4 MD	?	–	+	–	P
5	?	–	+	MV cordal rupture	P
6	?	–	+	MV cordal rupture	P
7 MS	?	–	+	–	NP
8 MS	?	–	+	–	P
9	+	–	+	–	NP
10 MD	+	–	+	–	NP
11 MD	+	–	+	–	NP
12 (fig 3)	–	Abnormal MV	–	Mycotic aneurysm MV and fistula	P

MD, myxomatous degeneration; MV, mitral valve; MS, mitral stenosis; P, performed; NP, not performed.

transducer was interfaced with a Hewlett-Packard imaging system (HP 77020 AC). All patients fasted for at least 4 hours. Premedication was not given and local anaesthetic (10% lignocaine) was sprayed into the patient's hypopharynx.[14] In the last 23 patients the tube was wrapped in a disposable sheath (International Medical) before the procedure. This did not cause any problems or image deterioration. An imaginary three dimensional outline of the defect was obtained from cross sections taken in different planes after careful tilting and repositioning of the transducer.

DEFINITION OF LESION

A vegetation was defined as a localised mobile mass of echoes contiguous with a valve leaflet or prosthetic valve (figs 1 and 2).

Cordal rupture was defined as a systolic whipping motion of an affected mitral leaflet tip within the left atrial cavity with loss of normal leaflet apposition.

Cusp perforation was recognised as an interruption of echoes in an aortic cusp (fig 2) or Hancock valve (see fig 4).

Abscess was defined as an abnormal echolucent area within the perivalvar tissue without communication with the circulation.

Mycotic aneurysm presented as an abnormal pulsatile echo-free protusion that was annular, supra-annular, or subannular (figs 1, 3, and 4).

Valve dehiscence presented as an echolucent area seen around the prosthetic valve ring resulting in open communication between two adjacent cavities (fig 1).

Results

Tables 1–3 summarise the findings at precordial and transoesophageal echocardiography and at operation.

NATIVE MITRAL VALVE (12 PATIENTS, TABLE 1)

Precordial echocardiography did not show a defect related to infective endocarditis in two patients. In six patients the images suggested the possibility of vegetations. Vegetations were positively identified in three patients. In one patient (case 12) the mitral valve was abnormal. Transoesophageal echocardiography showed valve abnormalities in all 12 patients, vegetations in nine, and complications in five. These data were confirmed at operation in seven patients. Five patients were successfully treated with antibiotics.

NATIVE AORTIC VALVE (NINE PATIENTS, TABLE 2)

Precordial echocardiographic studies did not show a defect in three patients. Vegetations were suspected in three patients and were definitely seen in three other patients. Signs of a complex abnormality were seen in three patients (patients 7–9).

Transoesophageal echocardiography identified the valve defect in all nine patients. Vegetations were seen in all and additional complications were identified in four (patients 5–8). In eight patients the data were confirmed at operation. The remaining patient (case 6) was successfully treated with antibiotics. The additional feature of perforation of the aortic cusp was missed in two patients with one or both techniques (patients 4, 5, and 9).

Table 2 Detection of vegetations or complications or both in patients with aortic valve endocarditis

Native aortic valve	Precordial echocardiography		Transoesophageal echocardiography		
Patient no	Vegetations	Complications	Vegetations	Complications	Operation
1	–	–	+	–	P
2	–	–	+	–	P
3 bicuspid	–	–	+	–	P
4	?	*	+	*	P
5 bicuspid (fig 2)	?	*	+	Aortic cusp perforation	P
6 bicuspid	?	–	+	Mycotic aneurysm posterior and subannular to aorta	NP
7	+	Abnormal MV	+	MV cordal rupture	P
8	+	Mycotic aneurysm anterior and supra-annular to aorta	+ +	Mycotic aneurysm anterior and supra-annular to aorta	P
9 bicuspid	+	Aortic cusp perforation	+	*	P

MV, mitral valve, P, performed; NP, not performed. *Aortic cusp perforation missed.

Table 3 Detection of vegetations or complications or both in patients with prosthetic valve endocarditis

Prosthetic valve Patient no	*Precordial echocardiography*		*Transoesophageal echocardiography*		*Operation*
	Vegetations	*Complications*	*Vegetations*	*Complications*	
1 M	–	–	+	–	P
2 M	–	–	+	–	NP
3 A	–	–	–	Valve dehiscence	P
4 A	–	–	–	Valve dehiscence	P
5 A	–	–	–	Valve dehiscence	P
6 A	–	–	+	Valve dehiscence and mycotic aneurysm posterior and subannular to aorta	P
7 A	–	Abnormal echo structure in LA?	–	Mycotic aneurysm posterior and subannular to aorta	P
8 A	–	Mycotic aneurysm posterior to aorta	–	Mycotic aneurysm posterior and subannular to aorta, and intramural abscess	*
9 MA	–	Mycotic aneurysm anterior to aorta	–	Valve dehiscence (A)	P
10 MAT (fig 1)	–	–	+	Mycotic aneurysm of M annulus	P
11 MAT	–	–	–	Valve dehiscence (M)	P
12 MAT (fig 4)	–	Mycotic aneurysm anterior to aorta	–	Mycotic aneurysm at the posterior aortic annulus and flail Hancock (M)	P

M, mitral prosthesis; A, aortic prosthesis; T, tricuspid prosthesis; LA, left atrium; P, performed; NP, not performed;
*Died, no necropsy.

PROSTHETIC VALVE (12 PATIENTS, TABLE 3)
Precordial echocardiography did not show any defect in eight patients. In one patient (case 7) an abnormal echo structure was noticed in the left atrium; the cause was not identified. In three patients (cases 8, 9, and 12) a mycotic aneurysm was found anterior to the aortic prothesis. Transoesophageal echocardiography showed vegetations in four patients: in three patients these were attached to the left atrial site of the mitral prosthesis and in one patient at the aortic valve ring. Complications were found in 10 patients: dehiscence of the posterior site of an aortic prosthesis in six; mycotic aneurysm in five; left ventricular free wall abscess in one patient; and a flail leaflet of a Hancock mitral prosthesis in one patient. The echocardiographic findings were confirmed at operation in 10 patients. One patient died (necropsy was not performed), and one patient was successfully treated with antibiotics.

Discussion

Infective endocarditis is potentially a life threatening disease. The need for operation in

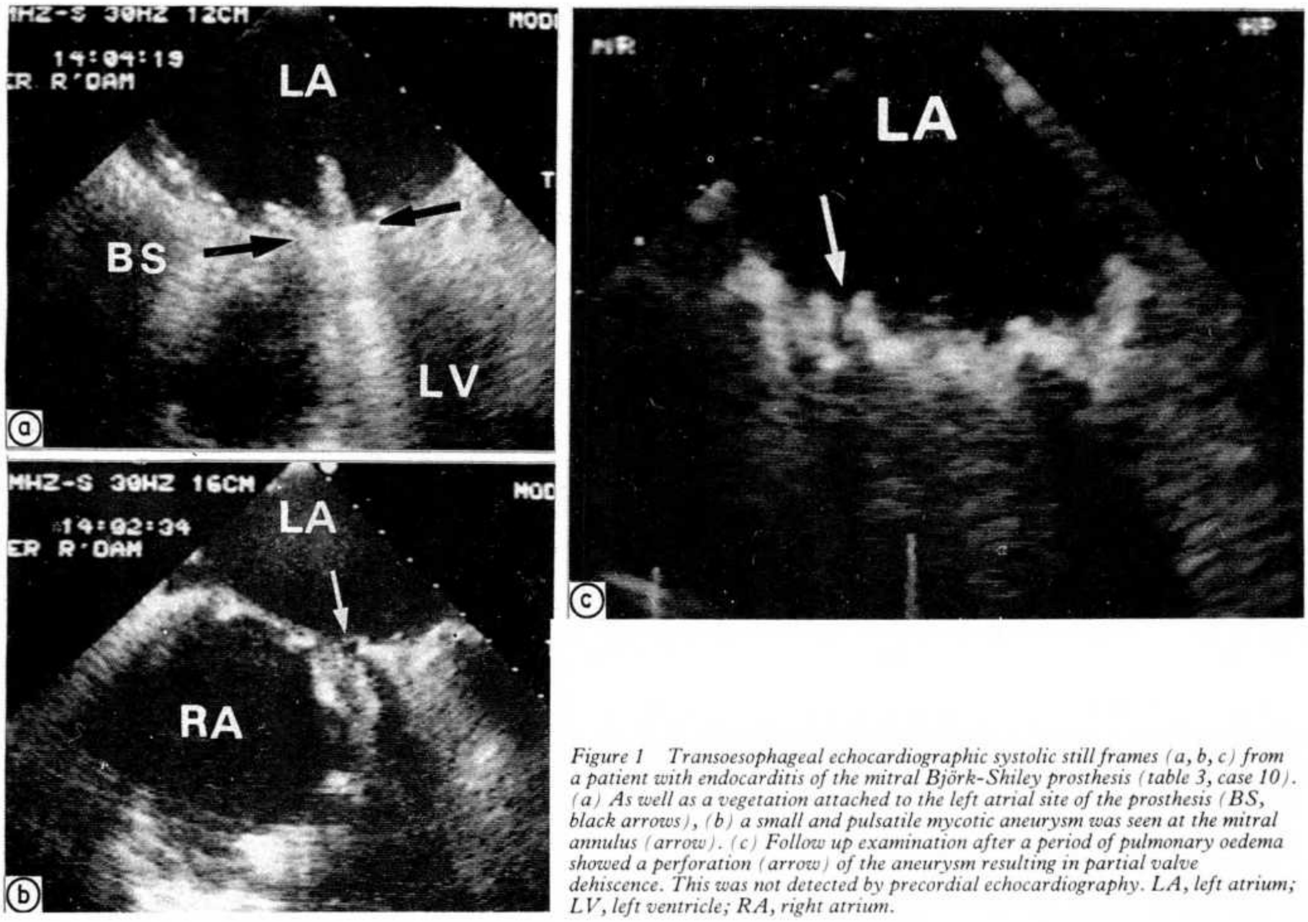

Figure 1 Transoesophageal echocardiographic systolic still frames (a, b, c) from a patient with endocarditis of the mitral Björk-Shiley prosthesis (table 3, case 10). (a) As well as a vegetation attached to the left atrial site of the prosthesis (BS, black arrows), (b) a small and pulsatile mycotic aneurysm was seen at the mitral annulus (arrow). (c) Follow up examination after a period of pulmonary oedema showed a perforation (arrow) of the aneurysm resulting in partial valve dehiscence. This was not detected by precordial echocardiography. LA, left atrium; LV, left ventricle; RA, right atrium.

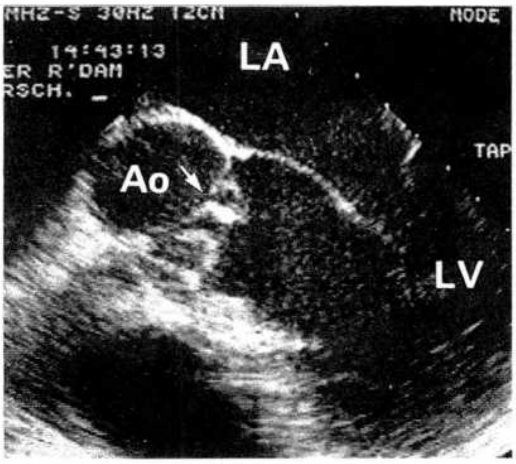

Figure 2 Transoesophageal echocardiographic diastolic still frame from a patient with endocarditis of a native aortic valve (table 2, case 5) showing a perforation in the aortic cusp (arrow) with a vegetation. This was not detected by precordial echocardiography. Ao, aorta; LA, left atrium; LV, left ventricle.

these patients usually indicates that the diagnosis and onset of treatment have been delayed.[15]

The incidence of detectable mycotic aneurysms or abscess formation during life is not known,[16] but these complications were often found in necropsy series.[17–19] Because perivalvar infective endocarditis is usually associated with a higher incidence of serious complications, a more complicated surgical procedure, or death[10 20 21] early diagnosis is essential.[22] But angiography proved to be of limited value.[6 10 23] Despite increasing experience in precordial echocardiography and the availability of more complex equipment, false negative studies in native valve endocarditis were reported.[4–6]

In patients with prosthetic valve endocarditis, the prosthesis can interfere with the ultrasound beam and ultrasound artefacts can hamper an adequate precordial study.[6 12] Limited resolution from the precordium also produced false positive images when there was pre-existing valve disease, which interferes with the precise visualisation of the underlying infectious process and any associated complications.[1–3]

The proximity of the transducer to the heart and avoidance of chest wall interference during transoesophageal echocardiography allows the use of a high frequency beam and this gives images of high resolution[24–26] showing the precise shape of the cardiac defect.

In all 33 patients in this study with clinically suspected endocarditis transoesophageal echocardiography (with a 5·6 MHz transducer) detected vegetations or complications or both. Using a 3·5 MHz transoesophageal transducer Daniel and co-workers achieved a detection rate of 85%.[13] With precordial echocardiography we detected valve defects in 30% of patients. Twenty five eventually underwent operation because transoesophageal echocardiography established the diagnosis without preoperative angiography.

The findings at operation show that false positive diagnoses did not occur with transoesophageal echocardiography. The technique failed to show aortic cusp perforation in two patients. The explanation for this may be the combination of the size and position of the perforation within the aortic cusp. Neither medical management nor operation was influenced by the absence of this specific information. Though the information obtained with transoesophageal echocardiography in the eight unoperated patients could not be independently confirmed, the quality of the images meant that an unequivocal diagnosis was possible.

NATIVE VALVE ENDOCARDITIS

Transoesophageal echocardiography detected many more vegetations in patients with native valve endocarditis (86%) than precordial echocardiography (28%). Complications too were more often detected with transoesophageal echocardiography (48%) than precordial echocardiography (20%). Five distinct pathological features in native mitral valve endocarditis were seen only with transoesophageal echocardiography. These were (*a*) mitral valve stenosis with vegetations; (*b*) myxomatous degeneration of leaflets with vegetations; (*c*) cordal rupture with vegetations and (*d*) without vegetations, and (*e*) mycotic aneurysm with fistulous connection (fig 3).

Similarly, in patients with aortic valve endocarditis high resolution images showed vegetations on a bicuspid aortic valve. The precise origin and outline of mycotic aneurysms were clearly shown.

PROSTHETIC VALVE ENDOCARDITIS

Transoesophageal imaging showed the defect in all the patients whereas precordial echocardiography was successful in only a third. This is not surprising because when a prosthetic valve is present the transoesophageal approach avoids ultrasonic shadowing by the prosthesis. In four patients with prosthetic valve endocarditis transoesophageal echocardiography detected vegetations that were not depicted by the precordial approach.

Complications at the valve ring of a mitral prosthesis (fig 1) or posterior portion of the aortic prosthesis (fig 4) are well displayed by transoesophageal echocardiography. But in patients with an aortic valve prosthesis the anterior aortic root is best displayed by the precordial approach. This observation is highlighted in two patients (table 3, patients 9 and 12) in whom precordial echocardiography showed evidence of a mycotic aneurysm in front of an aortic prosthesis (fig 4). Transoesophageal echocardiography did not identify this defect, though a mycotic aneurysm in the posterior valve ring was diagnosed only by this technique (fig 4).

Transoesophageal echocardiographic images

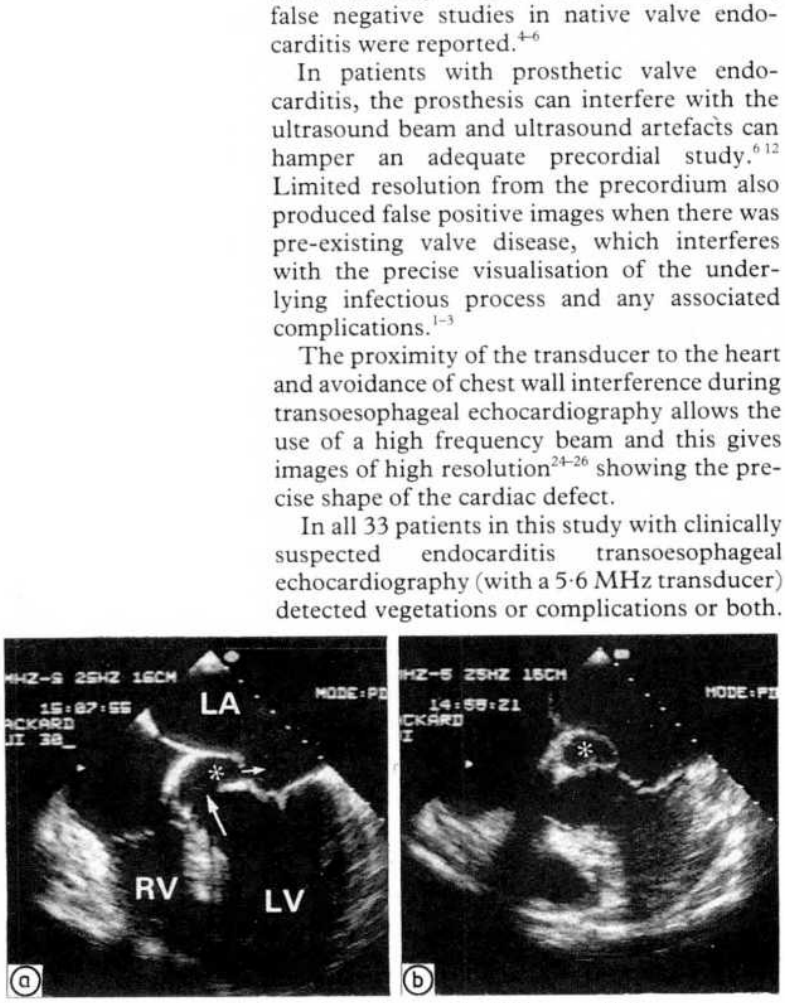

Figure 3 Transoesophageal echocardiographic systolic still frame (a, b) from a patient with endocarditis of the native mitral valve (table 1, case 12). (a) A subannular (to the aortic junction) mycotic aneurysm (asterisk) with a fistulous connection of the left ventricular outflow tract (large arrow) via the aneurysm into the left atrium (LA, small arrow). (b) Slight superior tilting of the transducer showed that there was no communication between the aneurysm and the left ventricle or left atrium. LV, left ventricle; RV, right ventricle.

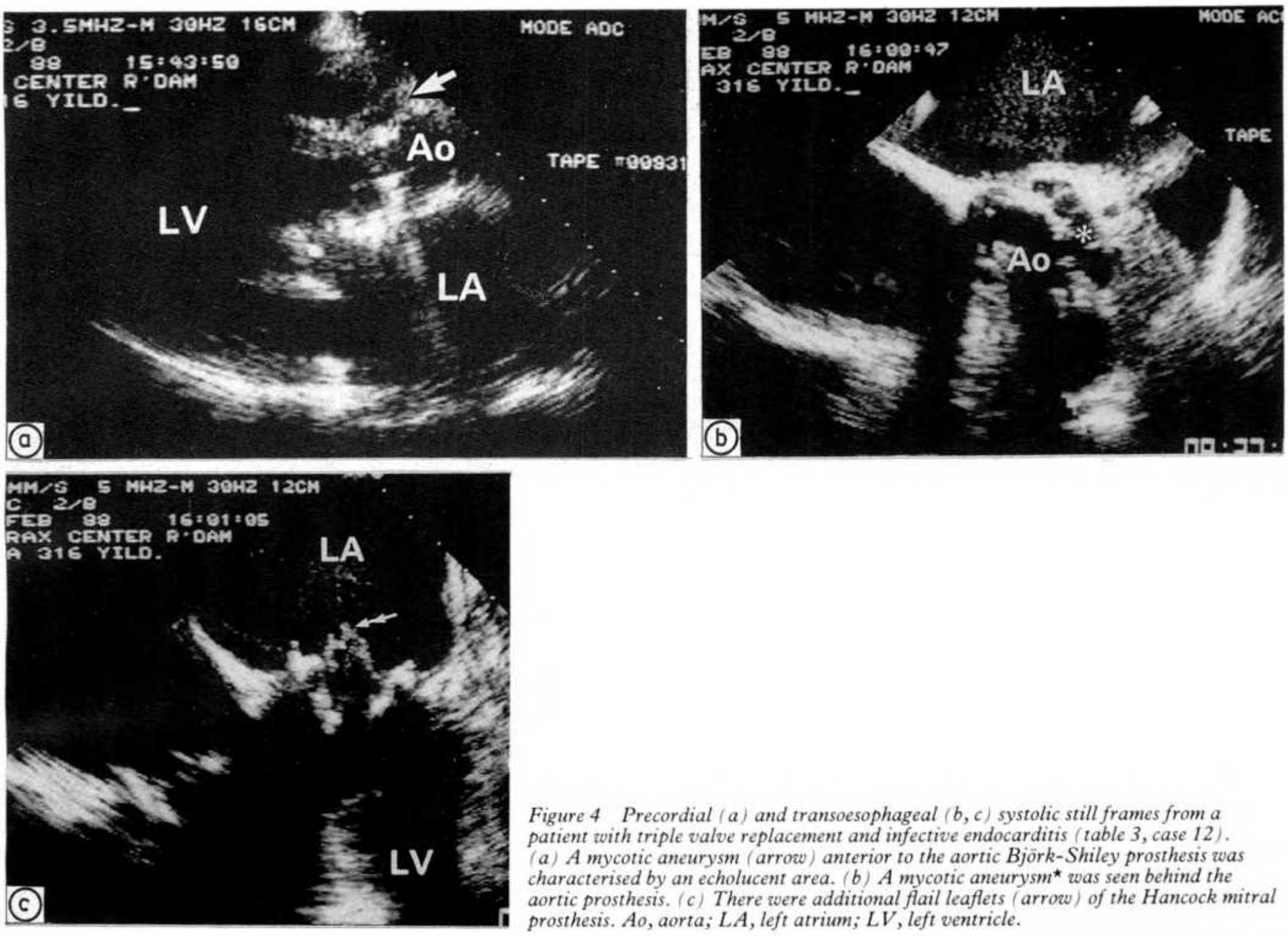

Figure 4 Precordial (a) and transoesophageal (b, c) systolic still frames from a patient with triple valve replacement and infective endocarditis (table 3, case 12). (a) A mycotic aneurysm (arrow) anterior to the aortic Björk-Shiley prosthesis was characterised by an echolucent area. (b) A mycotic aneurysm was seen behind the aortic prosthesis. (c) There were additional flail leaflets (arrow) of the Hancock mitral prosthesis. Ao, aorta; LA, left atrium; LV, left ventricle.*

were diagnostic and allowed appropriate decisions about clinical management in all patients. The technique was useful where clinical features suggested endocarditis and precordial echocardiographic imaging was either equivocal or negative. We think that transoesophageal echocardiography is the best diagnostic approach in patients with suspected endocarditis of either a native or prosthetic valve.

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Familial restrictive cardiomyopathy with atrioventricular block and skeletal myopathy

A P Fitzpatrick, L M Shapiro, A F Rickards, P A Poole-Wilson

Abstract

Five generations of an Italian family with an autosomal dominant restrictive cardiomyopathy are described. Members of four generations were examined. Symptoms usually developed in the third or fourth decade but the disease did occur in childhood. Initially the condition was characterised by normal ventricular size and systolic function with increased diastolic filling pressures in both ventricles and consequent bi-atrial enlargement. Cardiac catheterisation showed a left ventricular filling pattern of "dip and plateau". The electrocardiogram typically showed non-specific changes in the ST segment and T wave and changes indicating considerable atrial enlargement, which were confirmed by echocardiography. Light microscopy of two endocardial biopsy specimens showed no specific features but excluded the endomyocardial fibrosis of eosinophilic heart disease, amyloid, and specific heart muscle diseases. At necropsy in one case examined under light microscopy extensive patchy fibrosis was found throughout the endocardium, myocardium, and subepicardium, but there were no features typical of eosinophilic heart disease. Histopathological and biochemical examination of skeletal muscle identified no abnormality. The disease often had an insidious course over five to ten years after presentation. Bundle branch blocks, leading to complete atrioventricular block, however, often occurred and may be the first manifestation. Some individuals who survived into the fifth decade developed a progressive, non-wasting skeletal myopathy.

Restrictive cardiomyopathy gives rise to impaired compliance, impedance to ventricular diastolic filling, and cardiac failure. The best recognised cause of this abnormality is the spectrum of diseases encompassing Davies's endomyocardial fibrosis and Loffler's endocarditis.[1] Typically, in this restrictive cardiomyopathy there is gross endocardial fibrosis. This represents the end stage of a process that starts with inflammation, with eosinophilic infiltration, and myocardial necrosis.[2] Frequently there is endocardial thrombus formation, leading to thromboembolism. There may be involvement of the atrioventricular valves and cavity obliteration.[2] Other specific heart muscle disorders such as amyloid and haemochromatosis can also produce the haemodynamic characteristics of myocardial restriction.

We describe an hereditary disease producing features typical of ventricular restriction but without the gross endocardial changes usually seen. There was an associated but uncharacterised, non-wasting skeletal myopathy. The aetiology and pathogenesis are unknown.

Patients and methods

CLINICAL DATA

Two siblings (cases III.9 and III.10) received cardiac pacing for atrioventricular block. There was limited investigation at the time of pacing.

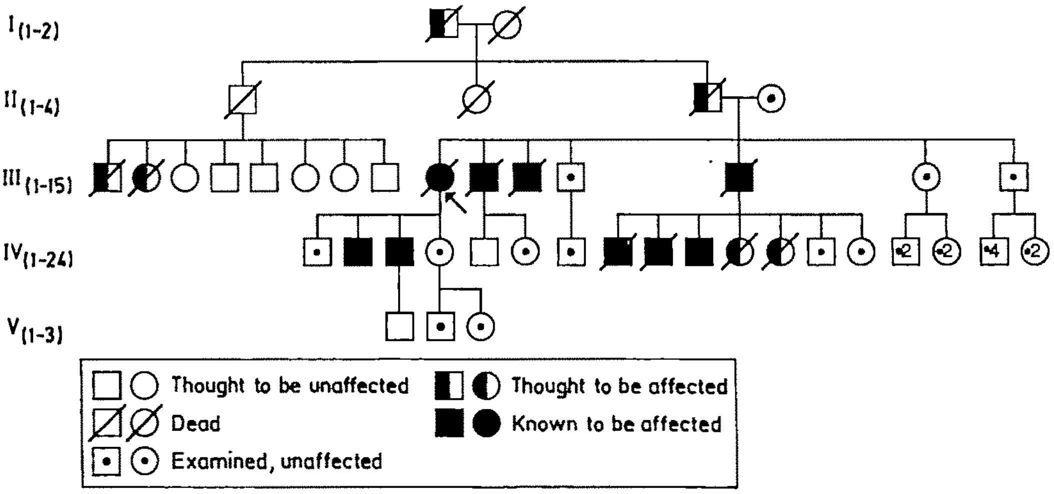

Figure 1 Family pedigree.

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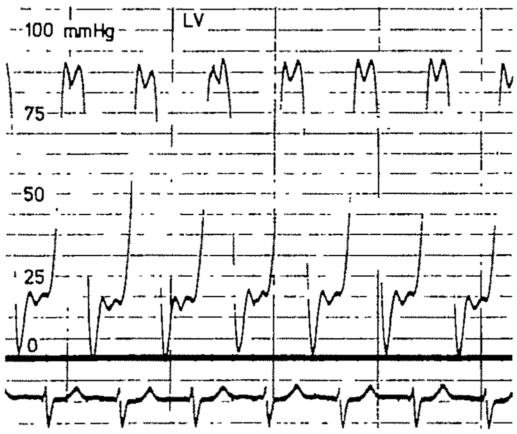

Figure 2 Left ventricular pressure trace in case III.10 showing a typical "dip and plateau" diastolic waveform of restrictive disease

With time similar cases presented among relatives. A detailed family history suggested an hereditary cardiac disease and we examined four generations of the family (fig 1). Members of a fifth generation (cases I.1 and I.2) are also described but were not examined. Cases III.9 and III.10 are described in detail. The table shows data on 15 confirmed or probable cases out of 48 family members in the pedigree.

Those who were examined and thought to be unaffected were symptom free individuals with normal physical examination and electrocardiography. One unaffected individual had a normal echocardiogram and skeletal muscle biopsy (case IV.1).

Case III.9

In 1974 a forty year old woman was referred for emergency cardiac pacing because of atrioventricular block. The electrocardiogram showed 2:1 second degree atrioventricular block and left atrial enlargement, which was confirmed by echocardiography. This also showed that ventricular systolic function was good. Cardiac catheterisation showed normal coronary arteries and normal ventricular size and function. Pressure traces were not available for review. Endomyocardial biopsy specimens were taken. These were examined by light microscopy only and showed regularly arranged myocardial fibres with mild hypertrophy. There was no endomyocardial fibrosis. Congo red staining for amyloid was negative.

After pacing she remained well for eight years but then became progressively disabled by a non-wasting myopathy affecting principally the proximal and distal muscles of her arms and legs, and also by exertional dyspnoea. Electromyography confirmed a primary muscle disorder without evidence of myotonia. Skeletal muscle obtained from the pectoralis major when the pacemaker pulse-generator was renewed showed some scanty fibrosis but no other histological abnormality. Biochemical analysis of this specimen showed higher activity of mitochondrial cytochrome oxidase than control specimens from the quadriceps. This may simply reflect differences in muscle fibre type. The activities of cytochrome oxidase and succinate cytochrome *c* reductase were normal, as was oxidation of pyruvate and palmitoyl carnitine. There was no evidence of carnitine deficiency or amyloid infiltration. She died suddenly in July 1988. Pacemaker function was normal.

Case III.10

In 1980 a forty one year old man was referred with dyspnoea and chest pain. The electrocardiogram showed right bundle branch block, left axis deviation, and first degree heart block with right atrial enlargement. There were non-specific abnormalities of the ST segment and T wave. Echocardiography showed global impairment of left and right ventricular systolic function with right ventricular hypertrophy and paradoxical septal motion. The right ventricle was enlarged but the left was of normal dimensions with impaired contraction. There was enlargement of both atria. At cardiac catheterisation contrast ventriculography showed poor systolic function of both ventricles. The coronary arteries were normal. All intracardiac pressures were raised and the left ventricular diastolic pressure showed the "dip and plateau" appearance often seen in myocardial restriction (fig 2). Endomyocardial biopsy specimens were taken from the left and right ventricles. These were examined under light microscopy only and showed no evidence of endomyocardial fibrosis. Congo red staining for deposition of amyloid was negative. Electrophysical studies showed normal atrioventricular conduction but in view of the family history permanent ventricular pacing was started.

In early 1987 a proximal left leg weakness developed and a biopsy specimen was taken of the quadriceps muscle. This showed some mild atrophy and fibrotic changes. A few abnormal fibres with dark staining edges were seen in trichrome and NADH stains. One vacuolated fibre was invaded by macrophages and contained fat globules. The activities of cytochrome oxidase and succinate cytochrome *c* reductase were normal as was oxidation of pyruvate and palmitoyl carnitine. Carnitine concentrations were normal.

He died suddenly in 1987. Necropsy showed some dilatation of all cardiac chambers but principally of the right atrium and ventricle. There was extensive patchy fibrosis in the epicardium, myocardium, and endocardium. The atrioventricular valves were not affected and endomyocardial fibrosis was not seen. The His bundle was extensively fibrosed. There was mild coronary atherosclerosis. Pacemaker function was normal.

Discussion

We found that symptoms associated with this restrictive cardiomyopathy usually developed in the third or fourth decade, though children might be affected. Asymptomatic ventricular restriction may occur before pulmonary venous hypertension leads to symptoms or before atrioventricular block intervenes. Skeletal muscle weakness may occur some years after the initial cardiac manifestations, usually in the fifth decade. Asymptomatic impairment of ventricular diastolic function with raised dia-

Clinical features and laboratory data in 15 individuals with restrictive cardiomyopathy

									Biopsy	
Case	*Sex*	*Age (D = Dead)*	*Symptoms*	*ECG*	*EMG*	*Echo*	*EPS*	*Catheter (mm Hg)*	*Endocardial*	*Skeletal*
I.1	M	43D	Sudden death	—	—	—	—	—	—	—
II.3	M	46D	SOB, proximal leg weakness	—	—	—	—	—	—	—
III.1	M	45D	Sudden death	—	—	—	—	—	—	—
III.2	F	37D	Sudden death	—	—	—	—	—	—	—
III.9	F	53D	SOB, severe proximal and distal arm and leg weakness	1974. 2 1 A-V block	Myopathy, excess polyphasic potentials	Left atrium +, left ventricular size and systolic function normal	AH 130 ms, HV 80 ms	Left ventriculogram normal, coronaries normal (no pressure traces)	Mild hypertrophy and fibrosis	Cytochrome oxidase increase, otherwise normal
III 10	M	46D	Chest pain, SOB, proximal and distal leg weakness	1980· RBBB, LAHB, RA + +, PR 220 ms, PRWP, ALST/TC	—	Right atrium +, right ventricle +, left atrium +, left and right ventricles poor systolic function	AH 100 ms, HV 80 ms	Left and right ventricular function poor, RAP $\overline{10}$, v = 25; PAP32/15/$\overline{27}$, PCWP $\overline{18}$, v = 24; RV 32/5/16; LV 125/12/20, dip and plateau diastolic waveform, mild coronary artery disease	Mild inflammatory changes	Normal light microscopy and mitochondial enzyme function
IV.8	M	18D	SOB	1979 LA +, RA +, LBBB, ALST/TC	—	—	—	RAP $\overline{17}$; RV 42/2/12, PCWP 18, v = 25; LV 115/—/34; no traces available	—	—
IV.9	M	15D	SOB, palpitation	1979. RA + +, LA +, ALST/TC	—	Left atrium + +, right atrium + +, left ventricular size and systolic function normal	—	RAP $\overline{8}$, RV 35/3/13; PAP 30/15 $\overline{23}$, PCWP $\overline{20}$ v = 25, LV 100/—/20; no traces available	—	—
IV 10	M	28	SOB, chest pain	1983 PRBBB, LA +, RA +, ALST/TC	—	—	—	—	—	—
IV II	F	6D	Sudden death	—	—	—	—	—	—	—
IV.12	F	16D	Sudden death	—	—	—	—	—	—	—
III.11	M	39D	Chest pain, SOB	1974: PRBBB, LAHB, PR 200 ms, ALST/TC	—	—	—	—	—	—
III.13	M	50D	Chest pain, SOB, proximal and distal R arm and leg weakness	1979 PRBBB, LAHB, PR normal, RA +, LA +, ALST/TC, 1982: LBBB, PR 200 ms	Myopathy, with spontaneous activity suggesting myotonia	—	—	—	—	—
IV.2	M	30	None	1985 LA +, ALST/TC, PRWP	—	Left atrium + right atrium +, right and left ventricular size and systolic function normal	AH 80 ms HV 30 ms	Left ventriculogram normal; RAP $\overline{7}$; RV 45/5/18, PAP 40/25/$\overline{33}$, PCWP $\overline{18}$, v = 25; LV 125/8/28; no dip and plateau, coronaries normal	—	Normal microscopy and mitochondrial enzyme function
IV.3	M	28	None	1988· LA +, ALST/TC	—	—	—	—	—	—

AH, conduction time from atrioventricular node to His bundle at intracardiac electrophysiological study, A-V, atrioventricular; ALST/TC, anterolateral ST segment and T wave changes on surface electrocardiogram; ECG, surface electrocardiogram, Echo, cross sectional and M mode echocardiography, EMG, electromyogram; EPS, intracardiac electrophysiological study; HV, conduction time from His bundle to ventricle; LA +, left atrial enlargement on surface electrocardiogram by voltage criteria (+ + very enlarged), LAHB; left anterior hemifascicular block; LBBB, left bundle branch block; LV, left ventricle; No traces available, pressure traces at cardiac catheterisation not available for analysis (all catheter pressures are in mm Hg as indicated), PAP, pulmonary artery pressures, PCWP, pulmonary capillary wedge pressures; PRWP, poor R wave progression in precordial leads; RA, right atrium, RAP, mean right atrial pressure, RBBB, right bundle branch block (PRBBB, partial block); RV, right ventricle, SOB, short of breath on exertion, v = height of v wave in PCWP.

stolic pressures may be the earliest manifestation of the disease. This was seen in case IV.2. In cases III.9 and III.10 symptoms of cardiac failure persisted for many years after initial presentation without evidence of ventricular dilatation.

Two cases occurred in childhood (IV.8 and IV.9) and two more children who died suddenly are thought to have had the disease (cases IV.11 and IV.12). In cases IV.8 and IV.9 the disease was rapidly-progressive leading to death in the second decade despite permanent pacing. Ventricular dimensions were normal although in cases III.10, IV.2, IV.8, and IV.9 both left- and right ventricular diastolic pressures were raised (table 1). Left ventricular systolic function may be preserved after symptoms have developed, as in case III.9. The extent and location of fibrosis may determine the clinical course—for example the development of atrioventricular block or pulmonary venous hypertension caused by raised left ventricular

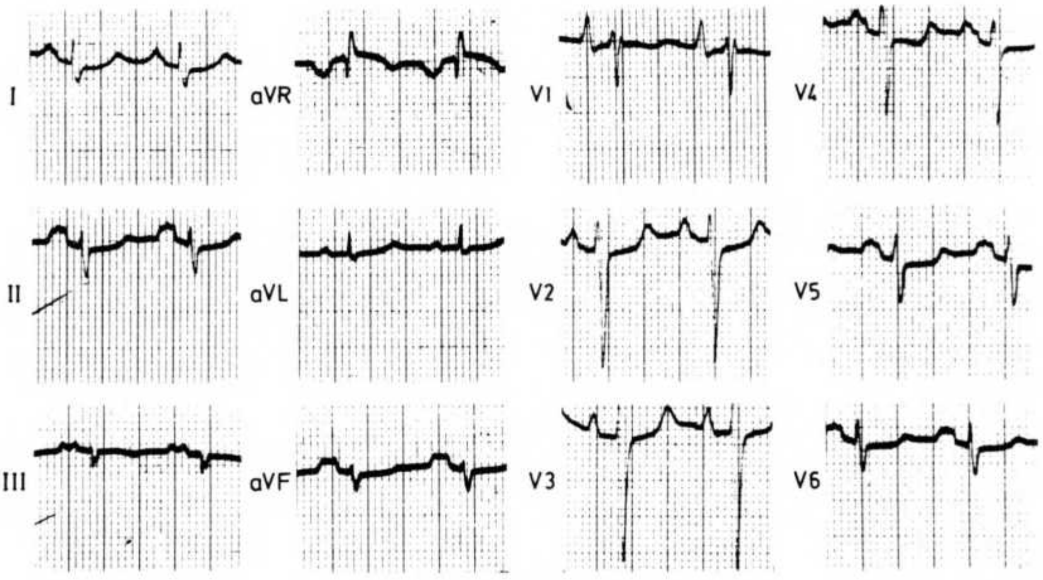

Figure 3 An electrocardiogram of case III.13 from 1979 showing incomplete right bundle branch block, left axis deviation, left and right atrial enlargement, and ST and T wave abnormalities.

diastolic pressure. Poor left ventricular systolic function develops late in the course of the disease as does the skeletal myopathy. Left ventricular dilatation is not an early feature, perhaps because fibrosis stiffens the myocardium.

The electrocardiographic features were striking. Typically, P waves were exceptionally tall in the right precordial leads and broad in the standard leads owing to considerable enlargement of both atria (fig 3); this was confirmed by echocardiography (fig 4). First degree atrioventricular block was often seen. There were often partial or complete bundle branch block patterns; and attenuation of precordial R wave progression, ST segment changes, and T wave abnormalities were common. Fibrosis in the conducting system accounts for the development of atrioventricular block. Electrophysiological studies were performed in three cases. In case III.9 there was clear evidence of prolongation of conduction times between the atrioventricular node and His bundle and the His bundle and ventricle. In case III.10 conduction times were normal but follow up after pacing showed that complete atrioventricular block had supervened. In the symptom free (case IV.2) electrophysiological studies were normal. The progress of disease in the conduction tissue was shown by changes in the surface electrocardiogram in case III.13. In 1979 the electrocardiogram showed partial right bundle branch block and left posterior fascicular block with a normal PR interval. Three years later there was complete left bundle branch block and first degree heart block.

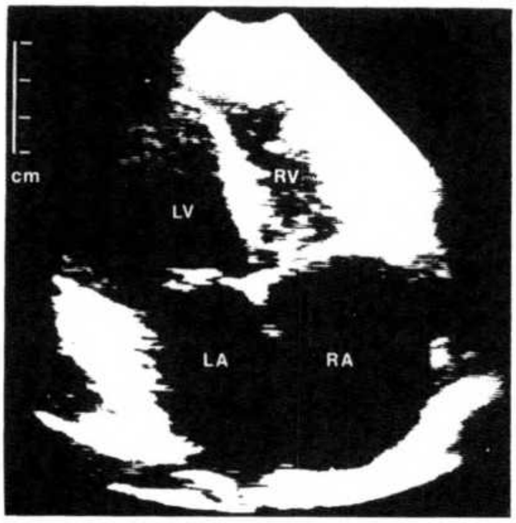

Figure 4 Cross sectional echocardiogram from an apical four chamber view showing biatrial enlargement (the right ventricle and atrium lie on the right in frame).

Extensive patchy fibrosis was found throughout the heart in case III.10. Gross endocardial fibrosis is the pattern more typically associated with endomyocardial fibrosis and eosinophilic heart disease. Loffler's endomyocarditis, with inflammation, eosinophilic infiltration, and necrosis may be the acute form of such eosinophilic heart disease.[1] Eosinophilia may be present at some stage in all cases of this type of restrictive cardiomyopathy, and D'Arbela *et al* recorded a mean survival of 24 months after presentation in one series.[3] In eosinophilic heart disease, because the fibrotic process is mainly confined to the endocardium, atrioventricular block is not a feature and skeletal muscle involvement has not been described. Eosinophilia was not found at any stage in any of this family and the disease clearly has an insidious course in most cases.

The pathogenesis of this condition is unknown. Endocardial biopsy specimens obtained from two patients at the time of initial investigation were subjected to only very limited histological examination. At that time the possibility of a familial cardiomyopathy had not been identified. Carnitine deficiency, which has been associated with familial cardiomyopathy,[4] was excluded in skeletal muscle specimens. Amyloid infiltration can produce impaired compliance[5 6] by stiffening the myocardium, but was not seen in any specimen. Other specific heart muscle disorders that have been associated with restrictive haemodynamic function are haemochromatosis[7] and collagen diseases such as scleroderma,[8] but there was no evidence of these diseases in the family we studied.

There are reports of similar cases to those in this family. Benotti *et al* described nine patients (from a retrospective analysis of cardiac catheterisation data) with restrictive ventricular diastolic pressure profiles and reported a good outcome.[9] Two endocardial biopsies were performed and in both the specimens were normal. Seigel *et al*[10] reported four cases of idiopathic restrictive cardiomyopathy with many similar features to this family. The disease was characterised by restrictive haemodynamic dysfunction, atrial dilatation, and, in one patient, the development of atrioventricular block. In this series the mean time of survival was nine years after cardiac symptoms had developed. Necropsies were performed in all four patients. There was no endomyocardial fibrosis typical of eosinophilic heart disease.[11] There was considerable dilatation of both atria and patchy endocardial fibrosis, with appreciable fibrotic infiltration of the myocardium that spared the atrioventricular valves. The patient with atrioventricular block had extensive His bundle fibrosis. None of these patients, however, is reported to have been related, nor does skeletal muscle weakness feature in these reports.

We report a familial disease of heart muscle producing myocardial restriction, apparently inherited as an autosomal dominant, and associated with atrioventricular block and a non-wasting skeletal myopathy. Heart block results from fibrosis in the conducting system. No endomyocardial fibrosis was seen, but fibrosis was found throughout the myocardium and epicardium at necropsy. This may be the end result of the pathological process and the cause of restriction.

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Cardiac involvement in congenital myotonic dystrophy

Håkan Forsberg, Bert-Ove Olofsson, Anders Eriksson, Staffan Andersson

Abstract

Seven young patients (mean age 19 years 8 months) with congenital myotonic dystrophy and with defined symptoms at birth were investigated by electrocardiography and echocardiography. None had cardiovascular symptoms. Electrocardiograms or echocardiograms or both were abnormal in all patients. Atrioventricular and intraventricular conduction defects were the most common electrocardiographic abnormalities and were seen in five patients. The echocardiographic examinations showed impaired left ventricular systolic function in one patient. Other echocardiographic findings were a small left ventricle and atrium, minor valve defects, and mitral valve prolapse.

This study shows that the heart is often affected in young patients with congenital myotonic dystrophy. The specialised conduction system is often affected and so too is the myocardium, causing impaired systolic function.

Myotonic dystrophy is a multisystem disease that is inherited in an autosomal dominant fashion at a locus on chromosome 19.[1] The disease is characterised by variable expression and severity, and symptoms usually appear when the patient is between 20 and 50 years old.[2] In adults the heart is often affected,[3] and the high incidence of sudden unexpected death, probably owing to arrhythmias or high degree atrioventricular block, is a major unsolved clinical problem in this disease.[4 5] Electrocardiographic and echocardiographic studies showed that the heart disease is progressive and that its severity corresponds to the severity of the neuromuscular disability.[6–8]

The term congenital myotonic dystrophy is applied to a subgroup of patients who have severe symptoms at birth. Newborn patients have respiratory and feeding problems, muscular hypotonia, and arthrogryphosis.[9] Neonatal mortality is high. In surviving children a severe form of myotonic dystrophy develops with both neuromuscular and intellectual disability.[10] The genetic defect in congenital myotonic dystrophy is inherited via the mother and the possibility of non-mendelian cytoplasmic transmission was suggested.[11 12]

We used electrocardiography and echocardiography to assess the extent to which the heart was affected in young patients with congenital myotonic dystrophy.

Patients and methods

We studied seven young patients with congenital myotonic dystrophy who fulfilled the diagnostic criteria of Volpe during the newborn period.[9] Table 1 shows some of the neonatal features in the patients. We studied all surviving patients with congenital myotonic dystrophy who had been diagnosed since 1970 at the Department of Paediatrics, Central Hospital, Boden, Sweden. This department serves the coastal region of Norrbotten, the northernmost province of Sweden, with 95 000 inhabitants and an exceptionally high prevalence of myotonic dystrophy.[7] The mean age of the patients was 19·7 years (range 11–27 years). Table 1 presents some additional clinical characteristics of the patients. There were two pairs of siblings (patients 2 and 3 and 6 and 7). Most patients were thinner than normal, and only one had a body mass index of >20 kg/m^2. Six patients had a straight or scoliotic thoracic spine and a short anteroposterior thoracic diameter.

The severity of the neuromuscular disability was classified on the basis of the patient's ability to perform those daily activities that can be limited by neuromuscular symptoms: *mild,* subjective symptoms but no functional disturbances; *moderate,* functional disturbances but the patient is able to undertake all activities of daily life and is able to do a light job; *severe,* major functional disturbances with the patient being incapable of undertaking most daily activities. Intellectual disability was classified according to the patient's ability to read ordinary texts: *mild,* minor reading difficulties; *moderate,* pronounced reading difficulties; *severe,* the patient was unable to read. The severity of neuromuscular disability was classified as mild in one, moderate in five, and severe in one of the patients; and the intellectual disability was classified as moderate in three and severe in four of the patients. None of the patients had any symptoms attributable to heart dysfunction or was taking medication known to induce electrocardiographic or echocardiographic changes. All patients had a normal blood pressure.

A 12 lead electrocardiogram (I, II, III, aVR, aVL, aVF, V1–V6) was recorded at a paper speed of 50 mm/s. The evaluation included a classification according to the Minnesota code[13] of arrhythmias, P wave amplitude, atrioventricular and intraventricular conduction defects, Q and QS patterns, hypertrophy patterns, ST elevation/depression, and T wave features. We used the criteria of Castellanos and Lemberg for fascicular blocks.[14] A P wave

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Table 1 Clinical characteristics of seven patients with congenital myotonic dystrophy

	Patient number						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Sex	F	F	M	F	F	F	M
Age (yr)	26	27	25	11	19	16	14
BMI (kg/m^2)	14·4	15·6	16·5	15·2	18·7	21·2	14·8
Severity of disease	Mod	Mod	Mod	Mild	Mod	Mod	S
Intellectual deficit	Mod	S	S	Mod	Mod	S	S
Maternal heredity	+	+	+	+	+	+	+
Neonatal features:							
Breathing problems	+	*	+	+	+	+	–
Feeding problems	*	+	+	+	+	+	+
Hypotonia	+	+	+	+	+	+	+
Facial diplegia	*	+	+	*	*	*	+
Arthrogryphosis	+	+	+	+	+	+	+
Thoracic deformity	+	+	+	–	+	+	+

BMI, body mass index, Mod, moderate; S, severe, *data not available.

of >0·13 mm was defined as broadened. The QT interval was corrected for differences in heart rate by a modification of Bazett's formula ($QTc = QT/\sqrt{RR}$, where the QTc interval is the corrected value of the QT interval and RR is the cardiac cycle length.[15]

An ATL Ultramark 8 sonograph (Advanced Technology Laboratories, Bothell, Washington, USA) was used for M mode, cross sectional, and Doppler echocardiography. The patients were examined lying on their left side and back while breathing quietly, and traces were obtained with the transducers in the parasternal, apical, and subcostal positions. M mode measurements were performed in accordance with the standards of the American Society of Echocardiography,[16] and the values obtained were compared with normal values presented by Henry *et al.*[17] Left ventricular systolic function was measured as fractional shortening (left ventricular end diastolic diameter minus left ventricular end systolic diameter divided by left ventricular end diastolic diameter). Right ventricular dimensions and systolic function were subjectively estimated as normal or abnormal. Mitral valve prolapse was diagnosed when the criteria of Devereux *et al*[18] were fulfilled. We defined hyperrefractile myocardial echoes as strongly refractile myocardial echoes persisting in different projections or angulations at gain settings low enough to eliminate completely the echoes from the surrounding endocardium and myocardium.[19]

Table 2 Electrocardiographic findings in seven patients with congenital myotonic dystrophy

	Patient number						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Sinus rhythm	+	+	+	+	+	+	+
Extrasystoles	–	–	–	–	–	+	–
Heart rate (beats/min)	86	57	68	94	77	77	78
P wave	N	N	N	N	N	N	N
First degree AV block	+	+	+	–	–	+	+
PQ interval (s)	0·20	0·22	0·24	0·16	0·18	0·20	0·21
IV block	LBBB	LAFB	LAFB	–	LAFB	–	LPFB
QRS interval	0·13	0·11	0·10	0·08	0·08	0·09	0·09
QT interval (s)	0·37	0·42	0·40	0·30	0·34	0·39	0·37
QTc interval (s)	0·44	0·41	0·43	0·38	0·38	0·44	0·42
T wave	N	N	N	N	N	N	N
QRS axis (degrees)	±0	−40	−45	+90	−40	+80	+135
ST deviation	–	–	–	–	–	–	–

N, normal, AV, atrioventricular; IV, intraventricular, LBBB, left bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block

Table 3 Echocardiographic findings in seven patients with congenital myotonic dystrophy (abnormal results are underlined)

	Patient number						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Aortic diameter (mm)	25	22	24	18	22	20	19
Left atrial diameter (mm)	28	28	27	30	29	21	27
LVD(D) (mm)	40	40	38	33	32	41	39
LVD(S) (mm)	28	28	22	23	21	28	29
IVS (mm)	8	10	11	7	8	9	9
PWT (mm)	8	9	11	7	8	10	8
Fractional shortening (%)	30	30	42	30	34	32	26
Normal right ventricle	+	+	+	+	+	+	+
Valve abnormality	MR	MVP	TR	–	–	–	–
Hyperrefractile myocardial echoes	–	–	–	–	–	–	–

LVD(D), left ventricular end diastolic diameter, LVD(S), left ventricular systolic diameter; IVS, interventricular septal thickness; PWT, left ventricular posterior wall thickness, MR, mitral regurgitation, TR, tricuspid regurgitation; MVP, mitral valve prolapse.

Results

Table 2 shows the electrocardiographic findings. Six patients had abnormal electrocardiograms with atrioventricular or intraventricular conduction defects or both. First degree atrioventricular block was found in five, left anterior fascicular block in three, left bundle branch block in one, and left posterior fascicular block in one of the patients. There were combined atrioventricular and intraventricular conduction defects in four electrocardiograms. All patients had normal sinus rhythm; one had solitary supraventricular extrasystoles. Hypertrophy patterns, abnormal Q waves, prolonged QT intervals, or ST-T changes were not found.

Table 3 shows the echocardiographic findings. The echocardiograms were abnormal in all patients. The left ventricular end diastolic diameter was shorter than normal in three patients, and two of these also had a short left ventricular end systolic diameter. One of the patients showed decreased fractional shortening with normal left ventricular dimensions and no local hypokinesia. One echocardiogram fulfilled the criteria of mitral valve prolapse. Doppler echocardiography showed mitral regurgitation in one and tricuspid regurgitation in another of the patients. These regurgitations were minor, but in both cases sufficiently large to be classified as abnormal by the investigator. The patients with mitral valve abnormalities had normal left ventricular dimensions and fractional shortening, and the patient with tricuspid regurgitation had no signs of right ventricular abnormalities. None of the patients had wall hypertrophy, ventricular dilatation, pericardial effusions, or abnormal myocardial texture.

Discussion

Congenital myotonic dystrophy is a rare disorder. O'Brien and Harper estimated the prevalence as 1 per 100 000 inhabitants in Wales,[20] and Wesström *et al* reported an incidence of 1 per 3350 live births in Sweden.[21] Our seven patients live in a region with 95 000 inhabitants and an exceptionally high prevalence of myotonic dystrophy.[7] A high regional prevalence is a prerequisite of systematic studies; this may explain why the effect of congenital myotonic dystrophy on the heart has not been studied before. The absence of young children in our series is probably the result of genetic counselling during the past decades.

Our knowledge of the prevalence and features of the heart disease associated with myotonic dystrophy is based on electrocardiographic and echocardiographic studies of patients in whom symptoms generally started in adulthood. Occasional patients with congenital disease are probably included in these series, but usually these cannot be identified from patient data. Electrocardiographic abnormalities were reported in most patients with myotonic dystrophy.[3] We found, in a recent study, abnormal electrocardiograms in 63% of all patients and in 96% of those with severe neuromuscular disability.[7] Atrioventricular and intraventricular conduction defects were the most common abnormalities but atrial fibrillation, abnormal Q waves, and repolarisation abnormalities were found in patients with severe neuromuscular disability. Echocardiographic and radionuclide studies have shown that the myocardium is affected in some patients with myotonic dystrophy, causing ventricular wall hypertrophy, left ventricular dilatation, and reduced fractional shortening.[3,7,22] In another echocardiographic study of another 30 adult patients we found left ventricular dilatation in six (20%), decreased left ventricular systolic function in five (17%), and left ventricular hypertrophy in four (13%).[8] The frequency and severity of electrocardiographic and echocardiographic abnormalities increased with the increasing severity of neuromuscular disability.[7,8]

In this study we found electrocardiographic abnormalities in six out of seven patients with congenital myotonic dystrophy. The main electrocardiographic finding, a high prevalence of atrioventricular and intraventricular conduction defects, accords with previous findings in patients with onset of symptoms in adulthood. No electrocardiogram in this series showed atrial fibrillation, abnormal Q waves, or repolarisation abnormalities—all signs of myotonic dystrophy that occur in adults with severe myotonic dystrophy.[7] We found echocardiographic abnormalities in all seven patients. Myocardial involvement with decreased left ventricular systolic function was, however, found in only one of the patients. No echocardiogram showed left ventricular hypertrophy or left ventricular dilatation. The clinical significance of some of these echocardiographic changes such as subnormal left ventricular and atrial dimensions and minor valve regurgitation without other signs of heart dysfunction is unclear. Subnormal body mass indices and thoracic deformities may have contributed to these findings. Several groups have reported an increased prevalence of mitral valve prolapse in patients with myotonic dystrophy,[23,24] but we did not find any clear overrepresentation of this anomaly in our study. A putative causal association between myotonic dystrophy and mitral valve prolapse was also questioned because myxomatous degeneration of the mitral valve or localised myocardial dysfunction have not been reported in myotonic dystrophy.[5,25]

We found signs of electrocardiographic or echocardiographic signs of heart involvement in all the patients with congenital myotonic dystrophy that we examined. Conduction defects were the main electrocardiographic finding. There were signs of impaired left ventricular function in one of the patients. The course and clinical implications of these features remain to be investigated.

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Abnormalities of the spleen in relation to congenital malformations of the heart: a survey of necropsy findings in children

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Abstract

A series of 1042 reports of necropsies on children dying at Children's Hospital of Pittsburgh was reviewed. In each case, note was taken of the status of the spleen, the lobation of the lungs, the arrangement of the bronchi, the morphology of the atrial appendages, and the presence of any congenital malformations of the heart and great vessels and of any malformations of the abdominal organs. There was isomerism of the left atrial appendages in eight (0·77%), 13 (1·25%) showed isomerism of the right appendages, and seven (0·67%) had multiple spleens without having isomerism of the atrial appendages. Unexpectedly, a normal spleen was found in one patient with isomerism of the right appendages and also in a patient with isomerism of the left appendages. In one patient with isomeric left atrial appendages there was no spleen. The review showed that the morphology of the atrial appendages, and hence the arrangement of the atria, is not accurately predicted by the type of spleen. The arrangement of the atrial appendages is the most reliable guide to the recognised combinations of congenital cardiac malformations previously described as "splenic syndromes". Because there is no certain way of predicting all the malformations in patients with complex congenital heart disease, it is advisable to record separately for each patient the details of lobation of the lungs, the bronchial and atrial arrangement, anomalies of the heart and great vessels, the type of spleen, and any abnormal arrangement of the abdominal organs.

It is now well recognised that complex congenital malformations of the heart are associated with abnormalities of the spleen and abnormal arrangement of the other thoracoabdominal organs.[1–3] Although it became fashionable to call these cardiac syndromes "asplenia" and "polysplenia",[4] it has since become clear that these are imperfect terms to describe the heart and its contained anomalies. This is because some patients without spleens have the constellation of lesions expected in "polysplenia", whereas the malformations expected in "asplenia" can be found in patients with single or multiple spleens.[5 6] The presence of right or left isomerism of the atrial appendages[6–8] is a much more accurate guide to the characteristic syndromes. Furthermore, some patients with multiple spleens and left isomer-

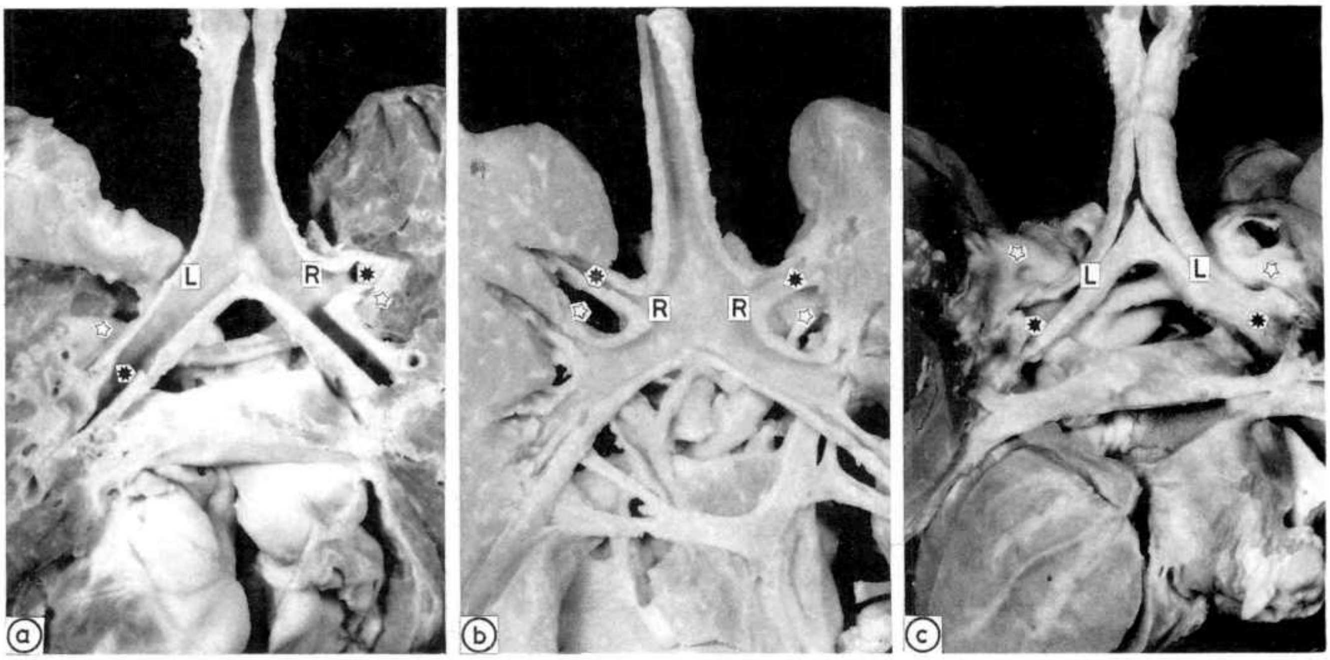

Figure 1 The arrangements of the bronchi are shown from behind in (a) a normal heart, (b) a heart with isomerism of the right bronchi, and (c) a heart with left bronchial isomerism. The left bronchus (L) is longer than the right (R). The morphologically left bronchus is below the pulmonary artery (hyparterial) while the morphologically right bronchus is above the artery (eparterial). Black star = bronchus; white star = pulmonary artery.

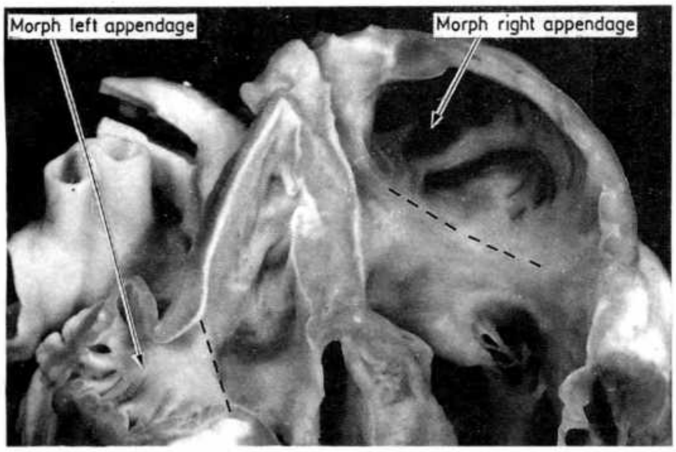

Figure 2 The normal heart is opened out to show the internal structures of the morphologically left and right atria. The tubular left atrial appendage has a narrow junction with the venous component of the atrium whereas the triangular right atrial appendage has a broad junction (dotted lines).

ism of the thoracic organs can have normally constructed hearts with the atria in their normal position.[1,9] But how common is this finding? And how frequently are accessory, as opposed to multiple, spleens encountered by the paediatric pathologist? These questions are vital for those who try to understand and categorise congenital malformations of the heart.[10,11] To answer them, we have reviewed the necropsy records from Children's Hospital of Pittsburgh over an 11 year period to ascertain the frequency and relation of abnormalities of the heart and thoracoabdominal organs.

Patients and methods

We examined the detailed reports on the 1158 necropsies carried out on children who died at the Children's Hospital of Pittsburgh from 1976 to 1986 inclusive. Of these reports, 116 were not included in the final analyses because the necropsy had either been exclusively thoracic or abdominal. We did not include two cases of conjoined twins because their hearts were fused.

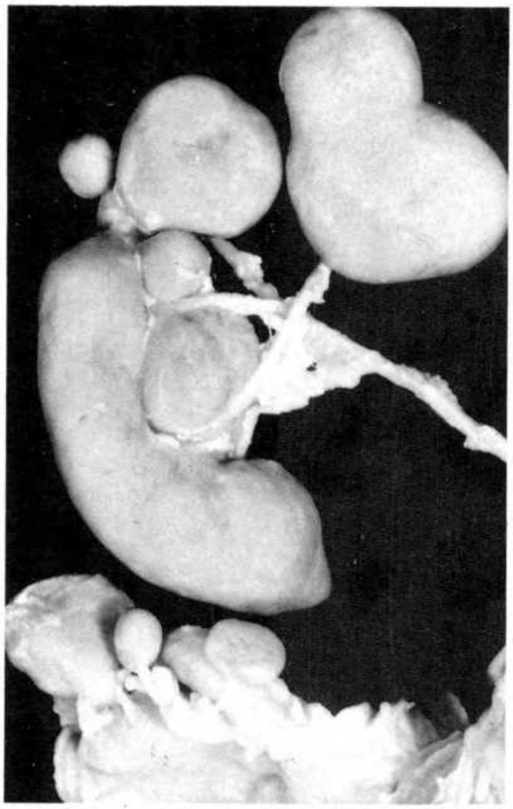

Figure 3 Multiple spleens.

We took information on the arrangement of the lungs, bronchi (fig 1), and atrial appendages (fig 2) from each report and noted any congenital abnormalities of the heart and great vessels. These structures were assumed to be normal if not specifically described to the contrary. The state of the spleen was recorded, as well as any evidence of abnormal arrangement of the other abdominal organs. The spleen was designated to be normal, absent, multiple (fig 3), or accompanied by accessory splenules (fig 4). Multiple spleens were recorded only when specifically described as such by the reporting pathologist. It was more common for additional splenic tissue, when noted, to be reported as accessory. The hearts of all the patients with isomerism of the atrial appendages had been retained in the Heart Museum. We re-examined these in sequential segmental fashion, making particular note of the venoatrial connections and any associated malformations (fig 5).

Results

Table 1 shows the general findings from the survey of the 1042 cases, broken down according to splenic morphology. According to the morphology of the atrial appendages, a total of eight patients (0·77%) in the overall series showed morphologically left isomerism (table 2) while 13 (1·25%) showed morphologically right isomerism (table 3). Another seven cases (0·67%) were discovered to have multiple spleens without any evidence of isomerism of the atrial appendages (table 4). There were no instances of complete absence of the spleen without left or right isomerism of the atrial appendages, but four cases had hypoplastic spleens (weighing, on average, 1·6 g). The spleen in one weighed only 0·6 g.

Five of the 116 incomplete reports are worthy of mention. Two were described as having "polysplenia", but a postmortem examination of the thoracic organs had not been performed to confirm the presence (or absence) of isomerism of the appendages. Another patient showed isomerism of the left atrial appendages and one isomerism of the right appendages, but no abdominal inspection had been carried out to record the state of the spleen. A fifth example of isomerism of the right appendages was noted in one of the conjoined twins. It is probable, therefore, that these cases would have increased the incidence of isomerism of the left and right appendages in the overall population.

Two of the 1042 cases had a mirror image atrial arrangement. Because the position of the lungs, bronchi, and abdominal organs showed appropriate mirror imagery these were all included in the category of those having normal spleens and lungs with attendant congenital heart disease.

There were 11 reports (1·06%) of accessory spleens accompanied by malrotation of the gut.

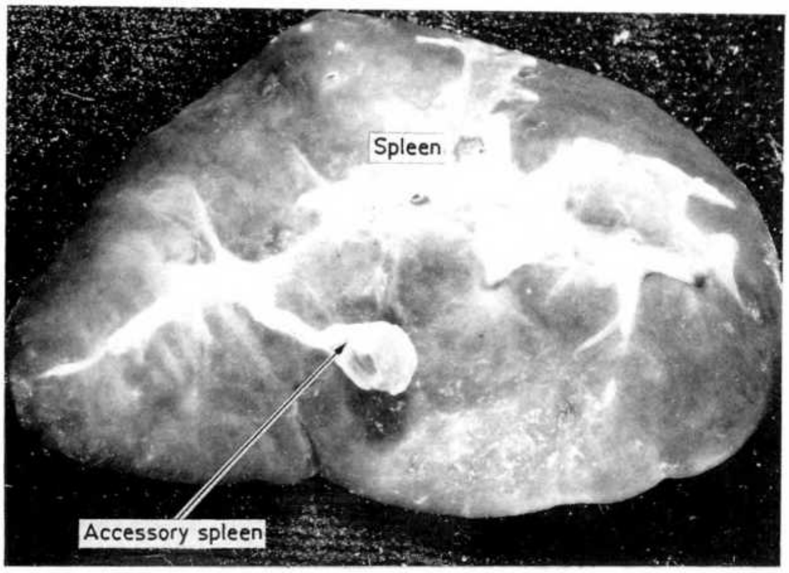

Figure 4 An accessory spleen.

One of these also had bilaterally bilobed lungs and hyparterial bronchi but all showed the usual atrial arrangement. Ten had diaphragmatic hernias, chromosomal disorders, or biliary atresia. Four cases had congenital heart disease, but not in the combinations expected for isomerism of the atrial appendages.

Isolated malrotation of the gut with a normal spleen was noted in 19 necropsies (1·82%). In 13 of these there were either diaphragmatic hernias or chromosomal disorders. Atrial arrangement was usual in all instances, with nine patients having some form of congenital heart disease. Abnormal lung lobation was mentioned twice, but neither patient had an isomeric arrangement of the bronchi.

Abnormalities of lobation of the lungs were reported in 80 cases (7·68%). Thirteen (1·25%) of these had bilaterally trilobed lungs (one case also having bilaterally eparterial bronchi). The spleen was normal in nine of these patients and the other four had accessory spleens. None had either form of isomerism of the atrial appendages or their cardiac manifestations. Forty four (4·22%) reports noted bilaterally bilobed lungs (four with accompanying bilaterally hyparterial bronchi). The spleen was normal in 35 of these patients, eight had accessory spleens, and the remaining patient had multiple spleens. None of these patients, however, had either isomerism of the left atrial appendages or the expected cardiac lesions.

Table 1 Summary of findings from 1042 necropsies

Categories		*No*	*% of total*
Cases of normal spleen:			
Normal lungs and normal heart		562	53·93
Normal lungs and abnormal heart		193	18·52
Abnormal lungs and normal heart		34	3·26
Abnormal lungs and abnormal heart*		37	3·55
	Total	*826*	*79·26*
Cases of accessory spleens:			
Normal lungs and normal heart		116	11·13
Normal lungs and abnormal heart		50	4·80
Abnormal lungs and normal heart		8	0·77
Abnormal lungs and abnormal heart		16	1·54
	Total	*190*	*18·24*
Cases of multiple spleens:			
Usual atrial arrangement		7	0·67
Left atrial isomerism		6	0·58
	Total	*13*	*1·25*
Cases of absent spleen:			
Right atrial isomerism		12	1·15
Left atrial iosomerism		1	0·10
	Total	*13*	*1·25*

*One case had right atrial isomerism.

Discussion

Our review of a large series of paediatric necropsies confirms our earlier predictions.[3,5] It is no longer reasonable to attempt to describe or diagnose congenital malformations of the heart in terms of abnormalities of the spleen. The attention given to the "splenic syndromes" has served its purpose in drawing attention to the cardiac malformations known to accompany them.

Our findings emphasise the relative constancy of the cardiac lesions themselves. Thus on the one hand there are hearts characterised by bilateral atrial appendages of right morphology. These hearts have bilateral superior caval veins, totally anomalous pulmonary venous connection, a common atrioventricular valve, and a high proportion of double inlet atrioventricular connection and an abnormal ventriculoarterial connection, usually with pulmonary stenosis or atresia.[1] On the other hand there are hearts with bilateral appendages of left morphology. These hearts characteristically have bilateral superior venae cavae (caval veins) and a common atrioventricular valve, but they have a relatively normal arrangement of their ventricular mass, coarctation rather than pulmonary atresia, and an anomalous connection of the inferior vena cava (caval vein), usually with azygos continuation.[2,8] The most accurate guide to the presence of these cardiac lesions is neither absence of the spleen nor the presence of multiple spleens. It is the existence of isomerism of the atrial appendages.[6]

When we describe "atrial isomerism", it should not be presumed that each atrium, along with its venous connections, is an isomer of the other. Far from it. The isomerism affects only the appendages, and these structures are truly isomeric. In this respect, it is the appendages that fulfil the criteria established by Van Praagh and his colleagues for determining the morphology of any cardiac chamber.[12] The principle they established[12] is called the morphologic method. In essence, it states that chambers within the heart should be identified according to their most constant components. It had been suggested that the inferior vena cava (caval vein) was the most constant atrial component, serving in this way to identify the morphologically right atrium.[13] The analysis of the present patients shows that this is not the case.

In our patients with abnormal arrangement of the abdominal organs, where it is most necessary accurately to determine atrial morphology, presence or absence of the inferior vena cava (caval vein) provides an ineffective marker of the morphologically right atrium. In contrast, all patients with the constellation of cardiac lesions previously known as "splenic syndromes" would have been correctly iden-

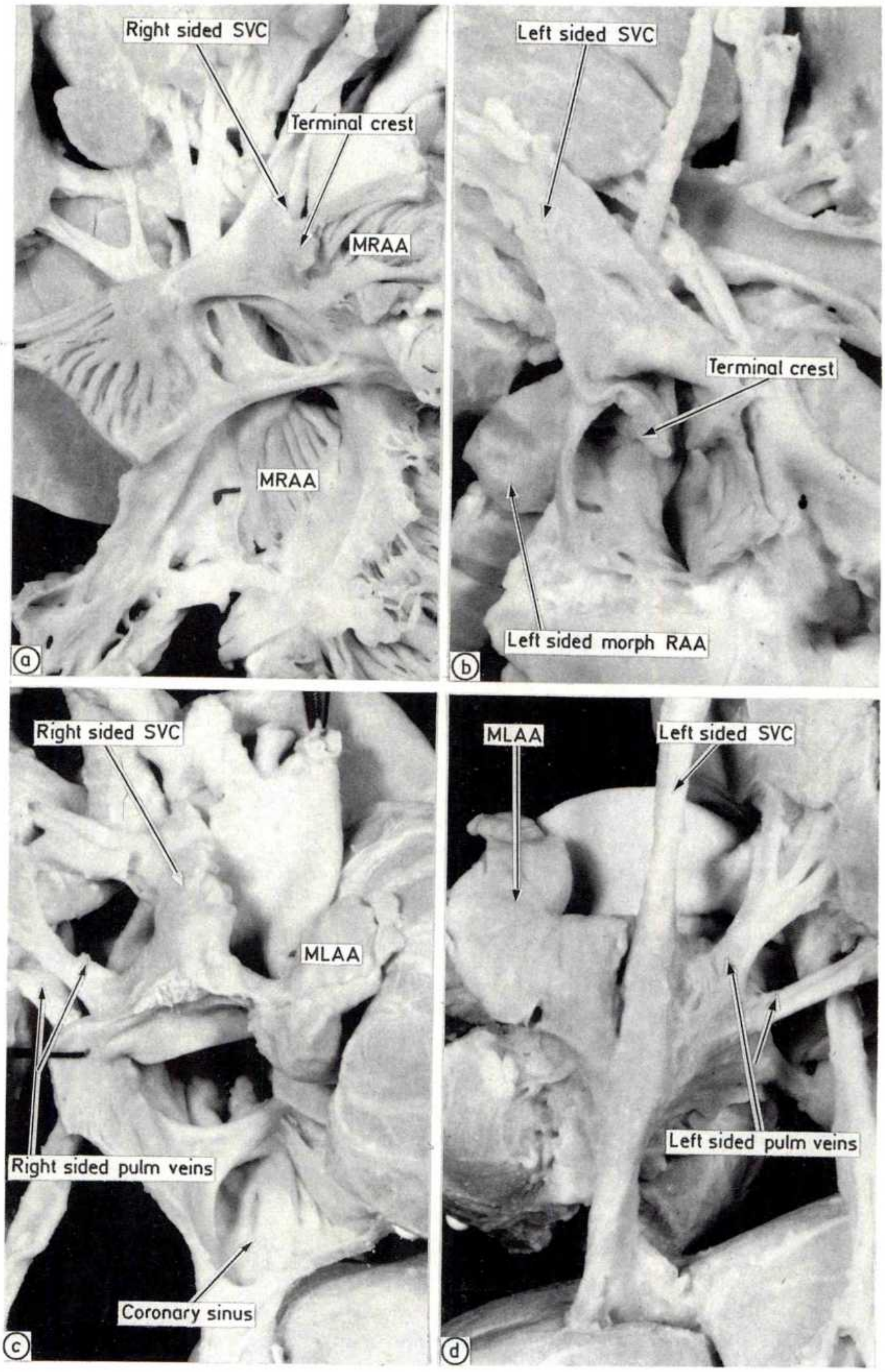

Figure 5 The top panels show a heart with isomerism of the right atrial appendages: (a) right sided atrium, (b) left sided atrium. Note the presence of bilateral venae cavae and terminal crests. The lower panels show the internal arrangement of the atria in the presence of isomerism of the left atrial appendages: (c) right sided atrium, (d) left sided atrium. Note the presence of bilateral superior venae cavae and pulmonary veins connecting directly to the atria. MRAA, morphologically right atrial appendage; RAA, right atrial appendage; morph, morphologically; MLAA, morphological left atrial appendage; pulm, pulmonary.

tified on the basis of isomerism of their atrial appendages. Thus the anatomy of the appendage and the arrangement of its junction with the venous atrial component provide an accurate means of distinguishing the morphologically right and left atria even in the presence of the most complex malformations of the heart. It is this criterion that best determines the arrangement of the atria. Furthermore, when the atria are abnormally formed in association with congenital cardiac anomalies, it is more accurate to describe them in terms of atrial isomerism rather than invoking considerations of malformations of the spleen.

Determining the arrangement of the atria is relatively easy for the pathologist, who holds the heart in his hands, and also for the cardiac surgeon, who can readily recognise the structure of the appendages as seen in the operating room. But what of the clinician, who is often

Table 2 Details of eight cases of isomerism of the left atrial appendages

Feature	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Right/left lung lobation	2 2	2 2	2 2	2 2	2 2	2 2	1 2	2 2
Bronchial arrangement	BH	BH	BH	BH	BH	BH	BH	BH
Spleen	Multiple 5	Multiple 9	Multiple 15	Multiple 12	Multiple 4	Multiple 7	Normal	Absent
Liver	Sym	L	Sym	Sym	L	Sym	Sym	R
Gallbladder	R	L	Mid	Mid	Mid	Mid	Mid	NK
Pancreas	Short mid	Glob mid	Glob	Glob mid	Short mid	Short mid	Glob	Glob
Stomach	R	L	L	L	L	L	R	R
Gut	Mal	Mal	Mal	Mal	Mal	Mal	Mal	Mal
Superior venae cavae	Bilateral	Bilateral L to CS to R-sided atrium	Bilateral	Bilateral L to L-sided atrium atretic R	Bilateral	Bilateral atretic left	L to L-sided atrium	R to R-sided atrium
Inferior vena cava	Bilateral SVCs & azy veins	Right to R-sided atrium	Azy cont to RSVC	Azy cont to LSVC	Azy cont to LSVC	Azy cont to RSVC	Azy cont to LSVC	Azy cont to RSVC
Hepatic veins	Confl to R-sided atrium	Bilateral	2 veins to R-sided atrium	Bilateral	Bilateral	Confl to L-sided atrium	Confl to R-sided atrium	Confl to R-sided atrium
Pulmonary veins	To L-sided atrium	To R-sided atrium	Bilateral	Bilateral	To L-sided atrium	To L-sided atrium	To R-sided atrium	To L-sided atrium
Position of heart	L	L	L	L	L	L	R	L
Apex of heart	L	L	L	L	L	L	R	L
Arterial relations	Normal	Normal	Normal	Normal	Normal	Normal	Mirror image	Normal
Atrial defects	Common atrium	Common atrium	Common atrium	Common atrium	Common atrium	Common atrium	Common atrium	Common atrium
Atrioventricular septal defect	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Atrioventricular valves	Common valve	Common valve	Common valve	2 valves	Common valve	Common valve	Common valve	Common valve
Ventricular septal defect	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Atrioventricular connection	Ambig	Ambig	Ambig	Ambig	Ambig	Ambig	Ambig	Ambig
Ventricular topology	RH	RH	RH	LH	RH	RH	LH	RH
Ventricular arterial connection	Concordant	Concordant	DORV	DORV	Concordant	Concordant	Concordant	Concordant
Pulmonary outflow tract	Patent	Patent	Musc subpulm stenosis	Patent	Valvar pulmon stenosis	Patent	Musc stenosis	Patent
Aortic outflow tract	Subaortic stenosis	Stenosis	Patent	Subaortic obstruct by tissue tag	Patent	Stenosis	Patent	Patent
Coarctation	Nil	Shelf	Nil	Isthmal hypo	Nil	Isthmal hypo	Nil	Isthmal hypo
Arterial duct	Ligament	Patent	Ligament	Patent	Ligament	Patent	Patent	Ligament
Aortic arch	L	L	L	L	L	L	R	L
Left ventricle	Normal	Hypo	Normal	Normal	Normal	Normal	Normal	Normal
Other malformations	Nil	Nil	R juxta atrial append	Nil	Nil	Nil	RV hypo	Nil

Ambig, ambiguous; append, appendages, azy cont, azygos continuation, BH, bilaterally hyparterial; Confl, confluent; CS, coronary sinus, DORV, double outlet right ventricle; Glob, globular; Hypo, hypoplasia; L, left; LH, left-hand; Ligament, ligamentous; LSVC, left superior vena cava; Mal, malrotation, Mid, midline, Musc, muscular, NK, not known; Obstruct, obstruction, Pulmon, pulmonary; R, right; RH, right-hand, R juxta, right juxtaposition of, RSVC, right superior vena cava, Subpulm, subpulmonary, Sym, symmetrical.

Table 3 Details of thirteen cases of isomerism of the right atrial appendages

Feature	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Right/left lung lobation	3 3	3 3	3 3	3 3	3 3	3 3	2 2	3 2
Bronchial arrangement	BE	BE	BE	BE	BE	BE	BE	BE
Spleen	Absent	Absent	Absent	Normal	Absent	Absent	Absent	Absent
Liver	Sym	Sym	L	Sym	Sym	R	Sym	Sym
Gallbladder	R	Mid	Mid	NK	NK	R	L	R
Pancreas	Short mid	Short mid	Glob mid	L	NK	R	R	Elong
Stomach	Mid	R	R	L	NK	R	R	NK
Gut	Mal	Mal	Mal	Normal	Mal	Mal	Mal	Mal
Superior venae cavae	Bilateral atretic right	L to L-sided atrium	Bilateral	Bilateral, L to L-sided A; atretic R	Bilateral	Bilateral	Bilateral atretic left	Bilateral
Inferior vena cava	To L-sided atrium	To R-sided atrium	To L-sided atrium	To L-sided atrium	To L-sided atrium	To R-sided atrium	To R-sided atrium	To L-sided atrium
Hepatic veins	Bilateral	To IVC	Bilateral	To IVC	To IVC	To IVC	To IVC	To IVC
Pulmonary veins	TAPVC Infradia	TAPVC to portal vein	TAPVC to RSVC	TAPVC to RSVC	TAPVC to portal vein	TAPVC R to portal L to LSVC	TAPVC to R-sided A	TAPVC to R-sided A
Position of heart	R	R	L	L	L	L	R	R
Apex of heart	R	R	L	L	L	L	R	R
Arterial relations	Aorta ant	Aorta to R	Aorta ant & right	Aorta ant	Aorta ant	Aorta to R side by side	Aorta ant	Aorta ant
Atrial defects	Oval fossa defect	Septal strand	Primum (AVSD)	Oval fossa defect	Oval fossa & primum (AVSD)	Common atrium	Oval fossa defect	Septal strand
Atrioventricular septal defect	Yes	Nil	Yes	Nil	Yes	Nil	Nil	Nil
Atrioventricular valves	Common valve	Common valve	Common valve	Common valve	Common valve	Common valve	Common valve	Common valve
Ventricular septal defect	Yes (AVSD)	Yes	Nil	Nil	Yes	Nil	Yes	Nil
Atrioventricular connection	Ambiguous	DIRV	Ambiguous	DIRV	Ambiguous	DILV	DILV	DIIV
Ventricular topology	LH	RH	RH	RH	RH	LH	LH	NA
Ventricular arterial connection	Discordant	DORV	DORV	Single outlet Ao from RV	Single outlet Ao from RV	Concordant	Single outlet Ao from RV	Single outlet Ao from IV
Pulmonary outflow tract	PA	Subpulm stenosis	Subpulm stenosis	PA	PA	PA	PA	PA
Aortic outflow tract	Patent	Patent	Patent	Patent	Patent	Patent	Patent	Patent
Coarctation	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Ductus arteriosus	Patent to confl PAs	Patent	Ligament	R-sided patent	R-sided patent	R-sided patent	R-sided patent	Ligament
Aortic arch	R	R	R	L	L	L	R	R
Left ventricle	Hypo	Slit-like	Hypo	Slit-like	Normal	Dominant	Normal	
Other malformations	Nil	Nil	Imperf LAVV	Nil	Nil	RV grossly hypo	Rudimentary RV	Solitary IV

Ant, anterior; Ao, aorta; AVSD, atrial or ventricular component of atrioventricular septal defect, BE, bilaterally hyparterial, DIIV, double inlet indeterminate ventricle; DILV, double inlet left ventricle, DIRV, double inlet right ventricle, Elong, elongated; IVC, inferior vena cava; Imperf LAVV, imperforate left atrioventricular valve; Infradia, infradiaphragmatic; IV, solitary and indeterminate ventricle, L-sided A, left-sided atrium, NA, not applicable; PA, pulmonary atresia, PAs, pulmonary arteries, R-sided A, right-sided atrium; RV, right ventricle; TAPVC, totally anomalous pulmonary venous connection

Table 4 Details of seven cases of multiple spleens and usual atrial arrangement

Case No	*Right lung lobation*	*Left lung lobation*	*Bronchial arrangement*	*No of spleens*	*Abnormal abdominal organs*	*Heart defects*	*Azygos continuation of inferior vena cava*	*Other malformations*
1	3	2	Usual	6	Globular pancreas, absent gallbladder	Nil	No	Biliary atresia
2	3	2	Usual	7	Globular midline pancreas, malrotated gut	ASD, Ao-pulmonary window	No	Biliary atresia
3	3	2	Usual	6	Malrotated gut	Nil	No	Pneumococcal septicaemia
4	3 + Acc	2 + Acc	Usual	4	Malformed stomach and pancreas	POF, ductus arteriosus, LSVC to CS	Yes	Diaphragmatic hernia
5	2	2	Usual	17	Absent gallbladder, short pancreas, malrotated gut	Nil	No	Biliary atresia
6	2	2	Bilat hypart	5	Globular midline pancreas, partially malrotated gut	Nil	Yes	Biliary atresia
7	2	1	Usual	9	Malformed pancreas, malrotated gut	POF	No	Arnold-Chiari malformation

Acc, accessory lobe; ASD, atrial septal defect, Ao-pulmonary, Aorto-pulmonary, Bilat hypart, bilaterally hyparterial; LSVC to CS, left superior vena cava to coronary sinus, POF, patent oval foramen

unable accurately to distinguish the morphology of the appendages and the nature of their junctions with the venous components. It is recognised that inferences must be made in these circumstances to permit the paediatric cardiologist to assess atrial arrangement, although it has been suggested that cross sectional echocardiography may, in skilled hands, permit direct recognition of the appendages. Similarly, if injections of contrast material are made into the atrial appendages, cineangiography permits direct diagnosis of atrial isomerism. None the less, if inferences are to be made, our analysis shows that bronchial morphology[14] is the best guide to the existence of isomerism of the atrial appendages. All but one case with atrial isomerism also had bronchial isomerism. The exception was a case of right atrial isomerism with usual bronchial arrangement. Five patients, however, were reported to have isomeric bronchi with usual atrial arrangement in the absence of any severe cardiac lesions. One of these cases was recently highlighted by Devine *et al*,[15] but our present analysis shows them to be more frequent than we thought. Despite these "false positives", bronchial anatomy remains by far the best inferential guide to the existence of the cardiac syndromes previously linked with (and named according to) splenic malformations. We found as many patients with multiple spleens with normal hearts as with isomerism of the left atrial appendages (previously described as "polysplenia"). Those with multiple spleens and usual atrial arrangement were usually examples of a syndrome known to exist with biliary atresia.[9] Their presence in such numbers in our series may reflect Pittsburgh's role as a major centre for liver transplantation. That, however, does not diminish the finding that multiple spleens can no longer be regarded as an accurate pointer to the presence of a specific syndrome of congenital heart disease. Although no patients without cardiac lesions had no spleen, four had such gross hypoplasia of splenic tissue that it was questionable whether the organ would have been demonstrable by clinical diagnostic techniques. Furthermore, one patient with isomeric right appendages had a normal spleen while another patient with isomeric left appendages had no spleen.

9	*10*	*11*	*12*	*13*
3 3	2 3	3 2	1 1	3 2
BE	Mirror image	BE	BE	BE
Absent	Absent	Absent	Absent	Absent
Sym	Sym	L	Sym	Sym
L	L	L	NK	L
NK	R	R	NK	R
L	R	R	NK	L
Mal	Mal	Mal	Normal	Mal
Bilateral	Right to R-sided atrium	Bilateral	Bilateral	Left to L-sided atrium
To L-sided atrium	L to L-sided atrium	To L-sided atrium	To R-sided atrium	To L-sided atrium
Bilateral	To IVC	Bilateral	To IVC	To IVC
TAPVC to portal vein	TAPVC to portal vein	TAPVC to R-sided A	TAPVC to R-sided A	TAPVC to R-sided A
R	R	R	R	R
R	R	R	R	R
Aorta ant & left	Aorta ant & left	Aorta ant & left	Aorta ant & left	Aorta ant
Primum (DIRV)	Septal strand	Primum (DILV)	Septal strand	Common atrium
Nil	Yes	Nil	Nil	Nil
Common valve	Common valve	Common valve	Common valve	Common valve
Nil	Yes	Yes	Yes	Yes
DIRV	Ambiguous	DILV	DILV	DILV
LH	LH	LH	LH	LH
DORV	DORV	Discordant	Single outlet Ao from RV	Single outlet Ao from RV
Subpulm stenosis	Subpulm stenosis	Severe subpulm stenosis	PA	PA
Patent	Patent	Patent	Patent	Patent
Nil	Nil	Nil	Nil	Nil
R-sided patent	R-sided patent	Patent	Patent	R-sided patent
R	R	R	L	R
Slit-like	Normal	Normal	Normal	Normal
Nil	Nil	RV hypo	RV hypo	RV hypo

The lesions previously correlated with splenic malformations are best diagnosed in terms of isomerism of the atrial appendages.[6] If diagnosis has to be made by inference, this will be achieved most accurately by referring to the pattern of bronchial morphology.[14] Splenic malformations are insufficiently well correlated with anomalies of the heart to justify their use either as an inferential guide or as a platform for nomenclature.

We thank Dr E Yunis, Director of Pediatric Pathology, who placed all the facilities of his department at our disposal, and the many pathologists who performed the initial necropsies, notably, Dr R Jaffe, Dr J Hubbard, Dr Y Hashida, and Dr S Taylor. During the course of their investigation, CA and RHA were on study leave from the National Heart and Lung Institute, University of London, and were supported by the Patrick Dick Memorial Fund, the British Heart Foundation, and the Joseph Levy Foundation

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Br Heart J 1990;63:129–31

CASE REPORTS

Pseudoaneurysm of the right ventricular outflow tract: diagnosis by colour flow mapping

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Abstract

Eleven years after surgical repair of pulmonary atresia with a ventricular septal defect with a valved conduit, a 20 year old patient was diagnosed on follow up echocardiography to have a right ventricular pseudoaneurysm related to the conduit. The echocardiographic findings were confirmed at reoperation and the pseudoaneurysm was excised.

A pseudoaneurysm of the right ventricle or right ventricular outflow tract is rare. Most reported cases presented either immediately after or within a few months of a right ventriculotomy.[1 2] The diagnosis in every reported case was confirmed by angiography or at necropsy. Pseudoaneurysms of the left ventricle are best defined by colour flow mapping.[3] We describe what we believe to be the first case of a right ventricular pseudoaneurysm in which the initial diagnosis was made by colour flow mapping.

Case report

At the age of nine this 20 year old woman had had complete repair of pulmonary atresia with ventricular septal defect. At operation the ventricular septal defect was closed and a valved conduit containing a 20 mm Hancock valve was inserted between the right ventricle and the main pulmonary artery. Routine cardiac catheterisation four years after operation showed a severely stenotic Hancock valve within a calcified conduit (right ventricle to pulmonary artery peak systolic gradient 100 mm Hg). Because the patient was symptom free at that time no further operation was contemplated. She remained symptom free over the next seven years until mild tiredness and intermittent sharp retrosternal pain unrelated to exercise developed.

Clinical examination showed no new signs. A prominent right ventricular impulse was palpable. An ejection systolic and early diastolic murmur (present seven years before) was heard in the pulmonary area. The chest *x* ray showed mild cardiomegaly. However, a striking new radiological abnormality was widening of the cardiac silhouette by a globular shadow in the region of the main pulmonary artery (fig 1). The electrocardiogram showed first degree atrioventricular block, a right bundle branch block pattern, and occasional atrial and ventricular extrasystoles. Cross sectional echocardiography showed severe right ventricular hypertrophy with abnormal motion of the interventricular septum. A large echo-free space was noted behind the thoracic wall; this was in front of and to the left of the right ventricular outflow tract. Imaging alone did not initially show a communication between this space and the right ventricle. Continuous wave Doppler examination confirmed a severely stenotic Hancock valve with peak systolic velocity in the conduit of 5 m/s. No flow was recorded within the echo-free space by pulsed Doppler. Colour flow mapping confirmed low velocity flow within this space. Detailed examination showed that this space communicated with the right ventricle through a narrow ostium sited beneath the Hancock valve (as shown by the colour flow map), confirming the diagnosis of pseudoaneurysm. Colour flow mapping also showed multiphasic turbulent flow across the ostium throughout the cardiac cycle (fig 2). Continuous and pulsed wave Doppler did not provide additional information: despite visualisation of the ostium, the peak velocities of flow could not be recorded because of the large angle between the ultrasound beam and the direction of flow as seen on the colour flow map. Bacterial endocarditis was excluded as a cause of the development of the pseudoaneurysm by repeated blood cultures, which were sterile.

Despite the unequivocal diagnosis by colour flow mapping, cardiac catheterisation was performed because the lesion is so rare. The right ventricular angiogram showed faint opacification of the pseudoaneurysm with contrast, presumably because it was large and the volume flowing to and fro during each cardiac cycle was low; no entry or exit point could be defined. The echocardiographic findings were confirmed at operation; the pseudoaneurysm was excised and the Hancock conduit replaced.

Discussion

A pseudoaneurysm results from a rupture of the ventricular wall with containment of the resultant haematoma by pericardium or extracardiac structures. Left ventricular pseudoaneurysms are known to occur after events such as myocardial infarction, ven-

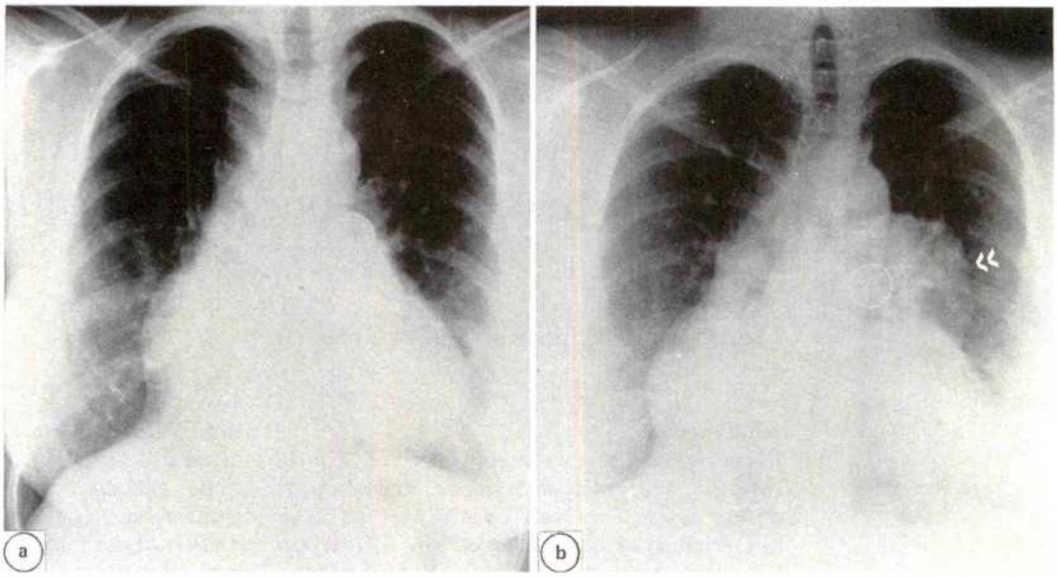

Figure 1 Chest x ray (a) showing the appearance four years before. The prosthetic valve ring was in the pulmonary position and there was mild cardiomegaly. (b) A new globular shadow along the left border of the cardiac silhouette (arrows) in the region of the main pulmonary artery.

triculotomy, chest trauma, infective endocarditis, or inflammatory processes affecting the heart.[4] Right ventricular pseudoaneurysms are less well described, and most of the few reported cases occurred within a few days or months of cardiac surgery, and were probably caused by surgical sequelae or endocarditis. Our patient had none of the above risk factors. In particular there was no evidence from the history or from subsequent investigations for bacterial endocarditis.

Left ventricular pseudoaneurysms are known to rupture even in the chronic stage. When right ventricular pressures are high, the risk of a rupture of right ventricular pseudoaneurysm may be similar. This, and the possibility of a successful outcome after surgical resection, means that prompt recognition of this lesion is important.[5] Angiocardiography is not without risk and is sometimes less than optimal.[6] In our patient the right ventricular angiogram failed adequately to opacify the pseudoaneurysm or show its ostium. The cross sectional features of pseudoaneurysm at echocardiography are well described; they include the demonstration of a saccular or globular aneurysmal chamber, a discontinuity of the endocardial image at the site of communication with the pseudoaneurysm, and a narrow orifice

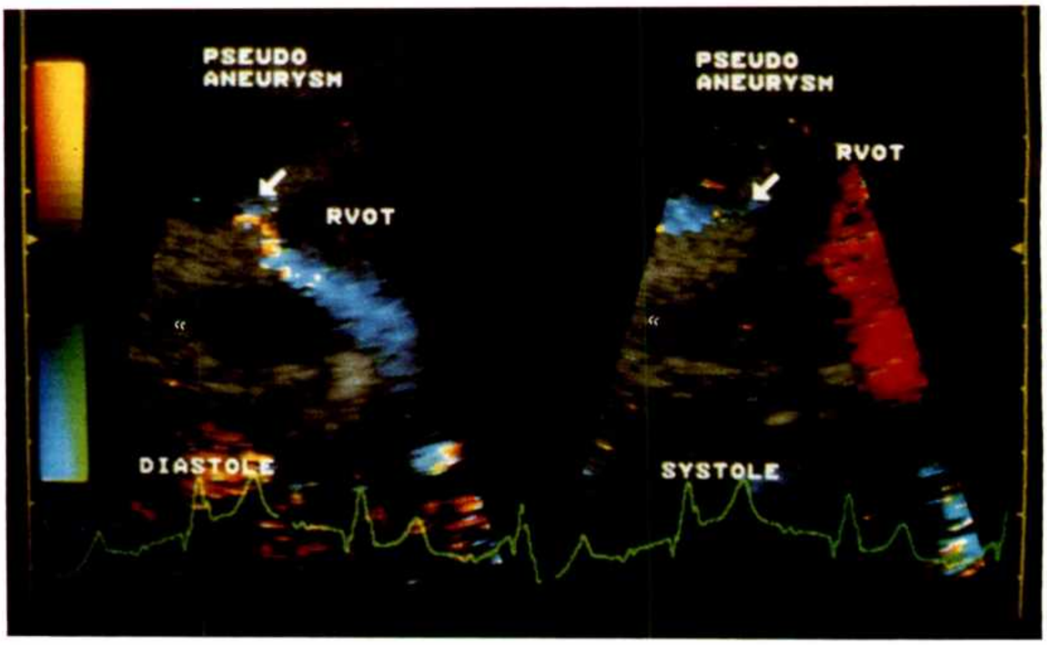

Figure 2 Cross sectional echocardiogram in the high parasternal view. Doppler colour flow map showing multiphasic flow into and out of the right ventricular pseudoaneurysm in different phases of the cardiac cycle (arrow). The pseudoaneurysm is represented by the large echo-free space at the top of the sector. The left hand panel shows diastolic flow from the pseudoaneurysm (arrow) in systole. The position of the prosthetic valve is indicated by the smaller double arrows. RVOT, right ventricular outflow tract.

diameter compared with the diameter of the aneurysm.[7] The diagnosis, however, hinges on the ability to show the ostium of the pseudoaneurysm. Pulsed and continuous wave Doppler may then be used to show turbulent high velocity flow through the restrictive ostium. Neither of these techniques proved helpful in our patient. A definite diagnosis was made only after colour flow mapping showed flow within the anterior echo-free space and identified the narrow communication between the right ventricular outflow tract and this space. The characteristic multiphasic pattern of turbulent flow described for left ventricular pseudoaneurysm was also noted in this case.[3] We believe that colour flow mapping may be the safest and most accurate investigative technique for diagnosing this rare lesion.

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Br Heart J 1990;63:132–3

Blood filled cyst of the papillary muscle of the mitral valve producing severe left ventricular outflow tract obstruction

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Abstract

A 46 year old man was found to have left ventricular outflow obstruction caused by a blood-filled cyst attached to the anterior papillary muscle of the mitral valve. It was successfully excised.

Small blood filled cysts of cardiac valves are commonly found in infants at necropsy, but are rare after the first year of life. They are believed to be cystic dilatations at the end of canals lined with endothelium in the substance of the valves.[1 2] We report a cyst of the mitral valve presenting as left ventricular outflow obstruction in an adult; it was successfully resected.

Case report

A 46 year old farmer gave a 5 year history of chest tightness and mild faintness on heavy exertion such as playing hockey or lifting bales of hay. There was no history of syncope. He had not had rheumatic fever.

On examination he was of lean build, apyrexial, and there was no finger clubbing. The pulse was regular but jerky. Blood pressure was 100/60 mm Hg. There was a systolic thrill palpable over the left sternal edge. There was a loud, harsh ejection systolic murmur heard throughout the precordium but greatest at the left sternal edge. It did not radiate to the carotid arteries.

The electrocardiogram showed sinus rhythm, an axis of +45°, left ventricular hypertrophy (S wave in V2 and R wave in V5 = 6 mV with no T wave changes), and no left atrial hypertrophy. The chest *x* ray showed a cardiothoracic ratio of 50%, but this had increased from 44% five years earlier. There was no prominence of the ascending aorta or left atrium. The haemoglobin concentration was 152 g/l, the erythrocyte sedimentation rate was 2 mm/h, and serum protein electrophoresis was normal.

Echocardiography showed an aortic valve that was not thickened or disorganised but showed prominent early systolic closure (fig 1a). There was a non-rheumatic mitral valve with systolic anterior motion of the anterior leaflet (fig 1b). There was mild concentric left ventricular hypertrophy. Cross sectional echocardiography showed a spherical mass (2·4 cm in diameter) with an echolucent centre within the left ventricular cavity (fig 2). It seemed to be attached to the anterior leaflet of the mitral valve. In systole it prolapsed into the left ventricular outflow tract. The cyst wall could be seen on the M mode echocardiogram as a fine echo abutting the septum (fig 1b). Doppler studies showed a turbulent high velocity systolic jet within the left ventricular outflow tract and no mitral regurgitation was detected.

At cardiac catheterisation the pulmonary capillary wedge pressure was 24/8 mm Hg, mean 16. The pulmonary artery pressure was 44/24 mm Hg, mean 24. There was no mitral valve gradient. There was a gradient of 140 mm Hg across the left ventricular outflow tract, falling to 110 mm Hg after 0·3 mg of phenylephrine was given into the pulmonary artery. The withdrawal gradient across the left ventricular outflow tract was 140 mm Hg (left ventricle body 240/20, left ventricle outflow tract 100/20, and aorta 100/65). Left ventricular cineangiography showed a mobile spherical mass within the left ventricle moving

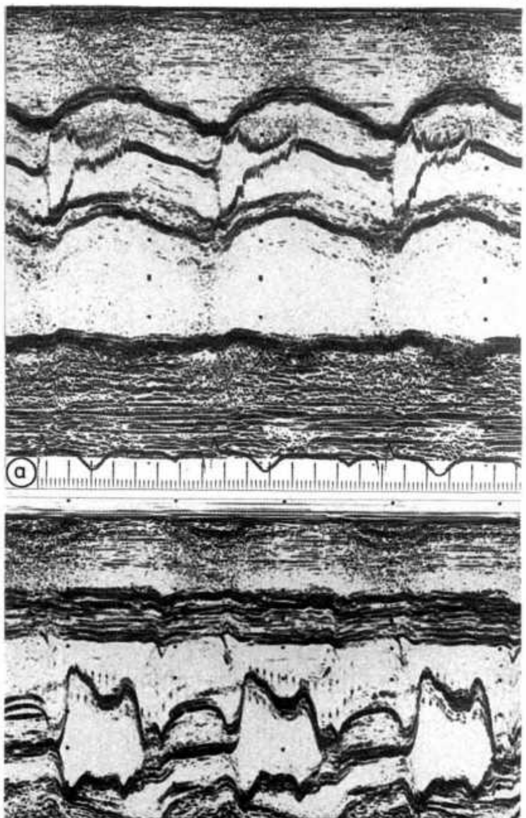

Figure 1 M mode echocardiograms showing parasternal views through (a) aortic root and (b) mitral valve.

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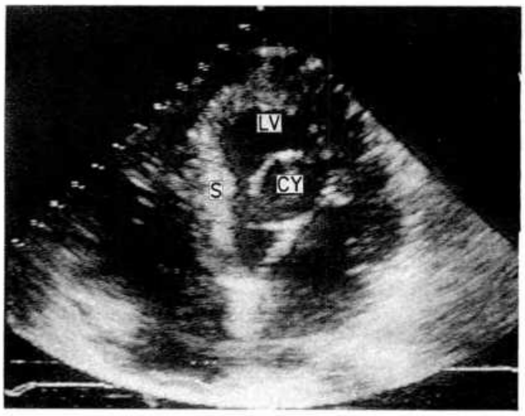

Figure 2 Cross sectional echocardiogram showing apical view. S, septum; LV, left ventricle; CY, cyst.

into the left ventricular outflow tract in systole. It seemed to be attached to the anterior leaflet of the mitral valve.

At operation, through an aortotomy, a smooth oval bluish mass (3·2 by 2·5 cm across), was found attached by a stalk to the tip of the anterior papillary muscle of the mitral valve. It was initially thought to be a tumour and to ensure complete clearance, the papillary muscle and anterior leaflet of the valve were excised through a standard left atrial approach and a 29 mm St Jude prosthesis was inserted.

The patient made an uneventful postoperative recovery and at follow up five months later was symptom free and working full time.

Histological examination showed a blood filled cyst, the wall of which was lined by an attenuated endothelium but with no evidence of epithelium. The wall itself was composed of fibrous tissue with no smooth muscle or organised elements within it.

Discussion

Leatherman *et al* reported the anatomical and pathological features of a blood cyst attached to the anterior leaflet of the mitral valve in a 39 year old woman that was successfully excised without requiring mitral valve replacement.[3] No outflow tract gradient was shown in their case.

Hauser *et al* reported a blood filled cyst attached to the tip of the anterolateral papillary muscle of the mitral valve in a 27 year old man that was successfully excised with the mitral valve.[4] The diagnosis was made on cross sectional echocardiography, and catheterisation was not performed. Liese *et al*, Cumming and Ferguson, and Jimenez-Martinez *et al* reported blood filled cysts attached to the pulmonary valve diagnosed at angiography and successfully excised at operation.[5-7]

Our patient presented with symptoms and signs suggestive of either severe mitral regurgitation or left ventricular outflow tract obstruction. Early closure of the aortic valve and systolic anterior movement of the mitral valve on M mode echocardiography suggested hypertrophic obstructive cardiomyopathy but the left ventricular hypertrophy was only mild and symmetrical. Cross sectional echocardiography showed that a most unusual spherical mass with echolucent centre attached to the mitral valve was the cause of the left ventricular outflow obstruction. The obstruction was confirmed by the demonstration of a 140 mm Hg gradient across the left ventricular outflow tract at catheterisation. The systolic anterior motion of the mitral valve may have been caused by a direct mechanical effect of the cyst pulling at its attachment rather than by the Venturi effect that is suggested to explain such motion in hypertrophic obstructive cardiomyopathy.

At operation the papillary muscle was excised to ensure adequate clearance of what was initially thought to be a vascular tumour. We suggest that the diagnosis of a blood-filled cyst should be considered if echocardiography shows a spherical mass with an echolucent centre; it may prove possible to remove it without the need to replace the mitral valve.

To our knowledge this is the first report of a simple blood cyst causing confirmed left ventricular outflow obstruction, and the second description of the echocardiographic features of such a cyst.

We thank Dr A Fletcher for his assistance with the histopathology.

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Gonococcal arthritis complicated by acute pericarditis and pericardial effusion

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Abstract

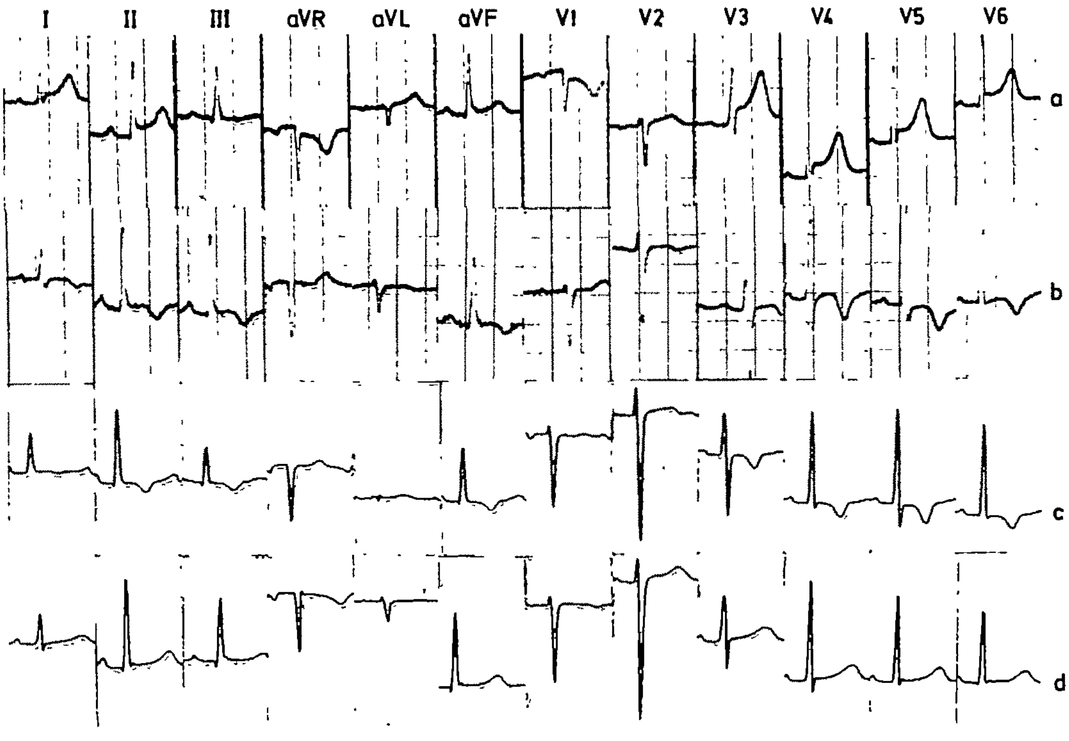
A woman of 23 presented with a painful, swollen left knee. A thick yellow fluid aspirated from the joint cavity grew *Neisseria gonorrhoeae*. Central pleuritic chest pain and ST segment elevation developed 48 hours after presentation. These signs and symptoms of pericarditis had settled two months after the acute illness.

We report a case of gonococcal arthritis associated with pericarditis. While on holiday in Southern France, a 23 year old white woman presented to a general hospital with a painful, swollen left knee. Before this, she had complained of a 3 day febrile illness associated with flitting arthralgia affecting the left knee, left elbow, and both shoulders. Clinical examination suggested a septic arthritis of the left knee, and the joint was explored. Thick yellow fluid with a high neutrophil count was aspirated from the joint cavity; a direct smear showed Gram negative intracellular diplococci, and subsequent culture grew *Neisseria gonorrhoeae*. She was treated with intravenous ampicillin and bed rest.

Forty eight hours later, she complained of central pleuritic chest pain and was found to have a pericardial rub. An electrocardiogram showed generalised ST segment elevation consistent with the diagnosis of acute pericarditis (figure a), and a chest *x* ray showed mild cardiomegaly only. A subsequent cross sectional echocardiogram showed a mild to moderate pericardial effusion but no other cardiac abnormality. Her symptoms were treated with aspirin and subsided within 48 hours.

Gynaecological examination was negative and no evidence of genital tract gonorrhoea was detected. The patient's boyfriend was also found to be negative and the patient did not report other sexual contact. The following investigations were found to be either negative or normal; vaginal, rectal, pharyngeal, and urine microbiology; blood culture; Venereal Disease Research Laboratory test; *Treponema pallidum* haemagluttination assay, hepatitis A and B; rheumatoid and antinuclear factors; antistreptolysin O and *Chlamydia trachomatis* titres.

The patient recovered over a period of four weeks, but required two weeks' stay in hospital. The electrocardiogram remained abnor-



Electrocardiographic tracing showing changes of pericarditis (a) on presentation and (b) one week, (c) six weeks, and (d) two months after presentation.

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mal both 1 week (figure b) and 6 weeks (figure c) after discharge from hospital. A repeat echocardiogram performed 2 months after the illness was normal, and by that time the electrocardiogram had also reverted to normal (figure d). All joint symptoms disappeared completely.

Discussion

Pericarditis in association with gonococcal arthritis has been infrequently described.[1–5] In some of these cases the diagnosis of pericarditis was based on an abnormal electrocardiogram rather than clinical presentation,[1 2 5] and this contrasts with our patient who had classic symptoms and signs of the disease. The electrocardiographic abnormalities of pericarditis have been found in disseminated gonococcal infection,[2 5] but are only rarely associated with the clinical manifestations, whereas some have found no electrocardiographic abnormalities at all.[6] Others suspected gonococcal pericarditis but were unable to obtain a positive bacteriological culture.[7–10]

The presence of pericardial effusion has also been infrequently noted, and in Boyle *et al*'s review of 414 cases of purulent pericarditis only two were associated with gonorrhoea.[7] The pericardial effusion in our patient was only mild to moderate and was not associated with a haemodynamic disturbance, so there was no clinical indication for pericardiocentesis. The nature of the pericardial fluid remains unknown but it did clear after successful treatment of the arthritis, and the follow up echocardiogram was completely normal and showed no evidence of pericardial thickening. Although purulent[7] and fibrinous[3] pericarditis have been described, the possibility of an allergic serositis[11] is not unlikely in our case. We found no published reports of the isolation of the organism from the pericardium, except in the presence of gonococcal endocarditis. Pericardiocentesis can therefore be recommended only for haemodynamic deterioration as a result of tamponade.

The diagnosis in this case was made simple by the positive cultures in the joint cavity, but the differential diagnosis of fever, polyarthralgia, and pericarditis includes diseases such as rheumatoid arthritis, systemic lupus erythematosus, Reiter's syndrome, hepatitis B infection, neoplasm, and other bacterial or viral infections. Primary gonococcal infection is often asymptomatic,[2] particularly in female patients and the diagnosis and appropriate investigation should be considered in patients presenting with such symptoms.

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Br Heart J 1990;**63**:136–40

Low pressure cardiac tamponade: diagnosis facilitated by Doppler echocardiography

Sharonne N Hayes, William K Freeman, Bernard J Gersh

Abstract

A case of low pressure cardiac tamponade is reported in which hypovolaemia altered the clinical findings of tamponade and complicated the diagnosis. Venous pressure was not raised and there was no pulsus paradoxus. In this patient, a man of 67, characteristic variations in diastolic inflow signals and the isovolumic relaxation period throughout the respiratory cycle were shown by Doppler echocardiography and led to the diagnosis of cardiac tamponade in the absence of characteristic signs and symptoms.

Cardiac tamponade is defined as cardiac compression caused by an accumulation of pericardial fluid that evokes and ultimately defeats compensatory mechanisms, resulting in haemodynamic compromise. Although the signs and symptoms of cardiac tamponade are relatively non-specific, the combination of dyspnoea, tachycardia, and hypotension with an almost universally raised central venous pressure and pulsus paradoxus usually leads the clinician strongly to suspect the diagnosis. We describe a patient in whom the signs and symptoms of tamponade were masked by hypovalaemia.

Case report

A 67 year old white man was admitted to the hospital after an episode of syncope with persistent hypotension. Thirteen days before admission, urgent coronary artery bypass surgery was performed for unstable angina. At that time, angiography showed moderate left ventricular dysfunction with an ejection fraction of 32% and severe occlusive disease of the right and left anterior descending coronary arteries. Saphenous vein grafting of the right coronary artery and left internal mammary grafting to the left anterior descending was uncomplicated. The patient was discharged five days before the current admission after an uneventful recovery. Discharge medications included aspirin 80 mg and a diuretic formulation of hydrochlorothiazide 25 mg and triamterene 50 mg, once daily.

The patient did not have any chest discomfort after operation. On the morning of admission, he experienced progressive dyspnoea and nausea, followed by an episode of syncope.

Evaluation in the local emergency room showed the patient to be tachycardic with a systolic blood pressure of 70 mm Hg. Intravenous dopamine (6 μg/kg/min infusion) and infusion of physiological saline transiently increased the systolic blood pressure to 90 mm Hg.

Upon transfer to our hospital, the patient was alert and complained of dyspnoea. Blood pressure was 80/60 mm Hg without pulsus paradoxus. The heart rate was regular at 110 beats/minute and the respiratory rate was 18/minute. The mucous membranes were dry, there was generalised pallor, and poor skin turgor. The lungs were clear and the sternotomy well healed. There was no jugular venous distension or Kussmaul's sign. The cardiac examination showed a grade 2/6 apical systolic murmur that radiated to the axilla suggestive of mild mitral regurgitation and a 2/6 systolic ejection murmur at the left lower sternal border. There was no rub, gallop, or extra sound.

The electrocardiogram showed sinus tachycardia, an old inferior Q wave infarction, and T wave inversion in leads V2–V6; all unchanged from the earlier postoperative tracings. The chest *x* ray showed moderate cardiomegaly and clear lung fields. The haemoglobin concentration and serum concentrations of creatine kinase and lactate dehydrogenase were within normal limits.

Intravenous infusion of one litre of physiological saline had no effect on the pulse or blood pressure; attempts to taper the

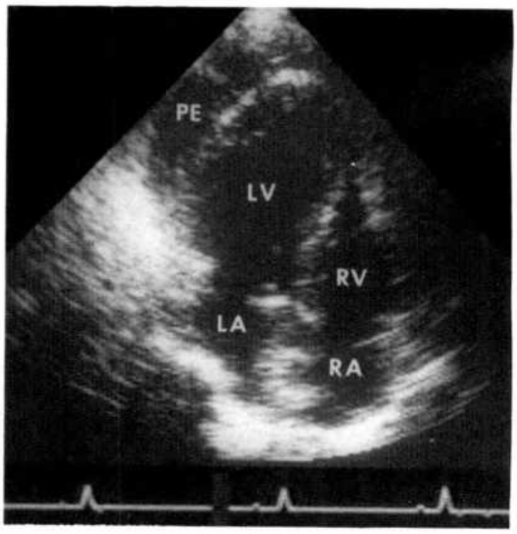

Figure 1 Four chamber cross sectional echocardiographic image of a moderate localised inferolateral apical pericardial effusion (PE). No diastolic compression of the free walls of the right ventricle (RV) or right atrium (RA) was evident. LV, left ventricle, LA, left atrium.

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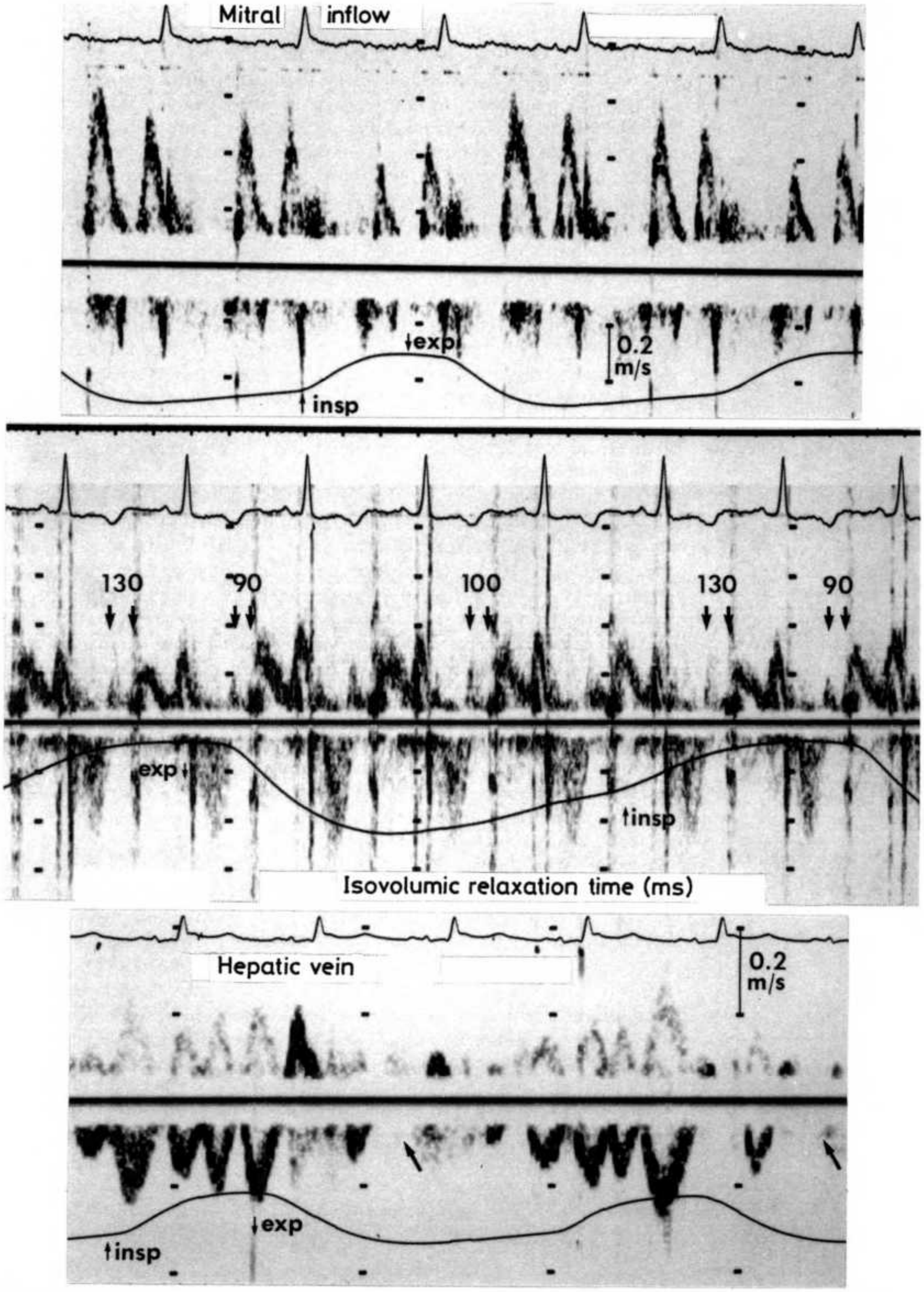

Figure 2 Pulsed wave Doppler findings before pericardiocentesis. Respirometry tracing indicates the onset of inspiration (insp) and expiration (exp). Early mitral inflow velocity fell with inspiration and increased considerably during the first beat after expiration. There was significant increase in isovolumic relaxation time (between pairs of arrows) with inspiration, with shortening occurring during the first beat after expiration. There was no diastolic hepatic venous filling (arrows) during the first beat after expiration.

dopamine infusion led to progressive hypotension.

Cross sectional echocardiography showed mild left ventricular enlargement with moderately decreased function and an estimated ejection fraction of 30–35% (similar to the preoperative study). The inferior septum was akinetic, with severe hypokinesis of the inferolateral segments from base to apex and moderate hypokinesis of the anteroseptal and anterior segments. There was a moderate localised inferolateral apical pericardial effusion with strands evident (fig 1). There was no diastolic compression of the right ventricular or atrial free walls.

Pulsed wave Doppler examination with respirometry showed a decrease of nearly 50% in mitral E wave velocity during early inspiration with accompanying prolongation of the isovolumic relaxation time. The velocity of the mitral E wave increased sharply with the first beat after expiration and the isovolumic relaxation time shortened. There was no hepatic venous diastolic filling during the first beat after expiration. These findings were consistent with cardiac tamponade (fig 2).

In view of the findings on physical examination that were discrepant with the echocardiographic diagnosis of tamponade, namely the absence of raised venous pressure or pulsus paradoxus, a balloon tipped catheter was placed in the pulmonary artery before pericardiocentesis. The zero reference point of the pressure transducer was the mid-chest, at the level of what we estimated to be the mid right atrium. As indicated in the table, diastolic pressure equilibration (10–11 mm Hg) was present. The slight increase in right atrial pressure contrasted with the clinical picture suggestive of systemic hypovolaemia. Infusion of a second litre of physiological saline did not result in an appreciable change in systemic or intracardiac pressures.

Pericardiocentesis, guided by cross sectional echocardiography, was then performed via a modified apical approach. The opening manometric intrapericardial pressure was raised (12 cm fluid) to the same extent as right atrial pressure. A 7 French pigtail catheter was passed into the pericardial space and 450 ml of dark serosanguinous fluid was evacuated. During fluid removal, the patient immediately noted a considerable improvement in his dyspnoea, the systemic blood pressure increased, and dopamine infusion could be stopped. Repeat haemodynamic measurements at the end of pericardiocentesis showed that the equilibration of diastolic pressure had disappeared and were consistent with appreciable hypovolaemia (right atrial pressure of 0 mm Hg); the stroke-volume index nearly doubled (table).

Percutaneous pericardial drainage was continued for another 48 hours and an additional 450 ml of fluid was removed without further accumulation. Analysis of the pericardial fluid showed a non-specific cell count; microbiology and cytology were negative.

A tiny residual pericardial effusion was detected on follow up cross sectional echocardiography. Pulsed wave Doppler showed no significant variation in mitral E wave inflow velocities or isovolumic relaxation time throughout the respiratory cycle, and expiratory diastolic hepatic venous filling had returned (fig 3).

The patient was discharged in excellent condition four days after admission. The patient's cardiopulmonary state was stable at four months follow up. Cross sectional echocardiography at that time showed no recurrent pericardial effusion; the results of pulsed wave Doppler with respirometry were unchanged from the study immediately after pericardiocentesis.

Discussion

Low pressure cardiac tamponade is caused by a compressive pericardial effusion when the intravascular blood volume is considerably depleted.[1] The central venous pressure is normal or often low, and hence the jugular venous distension, seen in classic tamponade, is absent.[1,2] Pulsus paradoxus, although dependent on pulse pressure, is another clinical sign of tamponade that is often absent when there is concomitant hypovolaemia.[1,2]

The differential diagnosis of this patient's low cardiac output state included myocardial dysfunction from infarction or ischaemia and a mechanical complication of coronary bypass surgery such as tamponade, pulmonary embolism, or hypovolaemia. Physical examination in this case was only partly informative, and atypical for cardiac tamponade.

Cross sectional echocardiography at the bedside identified a potential cause of the low cardiac output because it showed a moderate pericardial effusion with primary localisation along the inferolateral left ventricle. There was no excessive "swinging" motion of the heart or diastolic compression of the free wall of the right chamber. In this patient, the cross sectional echocardiogram was not at all diagnostic of tamponade; an inconsistency which has been previously recognised in postoperative pericardial effusions.[3]

In the absence of typical cross sectional findings of cardiac tamponade,[4–6] Doppler echocardiography was the crucial non-invasive method of reaching a diagnosis in this patient. Significant respiratory variation in mitral E wave velocity, isovolumic relaxation time, and loss of early expiratory diastolic systemic venous filling were detected by Doppler. These findings have been associated with cardiac tamponade.[7,8]

Appleton *et al* correlated the dissociation of pulmonary capillary wedge filling pressure and intrapericardial pressure during respiration with mitral inflow velocities measured by pulsed wave Doppler in cardiac tamponade.[7] During inspiration, pulmonary wedge pressure falls relative to intrapericardial pressure and so reduces the gradient between the left atrium and left ventricle in diastole. Because Doppler flow velocities are directly related to the driving pressure gradient, the early mitral E wave velocity also falls appreciably with the onset of inspiration. The isovolumic relaxation time also increases with inspiration, reflecting delay of mitral valve opening with the decrease in

Results of catheter studies

	Before pericardiocentesis	*After pericardiocentesis*
Heart rate (beats/min)	110	70
Pressure (mm Hg)		
Systemic arterial	70/50	100/60
Mean right atrial	10	0
Right ventricle	26/11	20/1
Pulmonary artery	25/11	20/2
Pulmonary capillary wedge	10	5
Cardiac index (l/min/m^2)	2 6	3·2
Stroke volume index (ml/beat/m^2)	24	46
Mean intrapericardial pressure (cm H_2O)	12	1

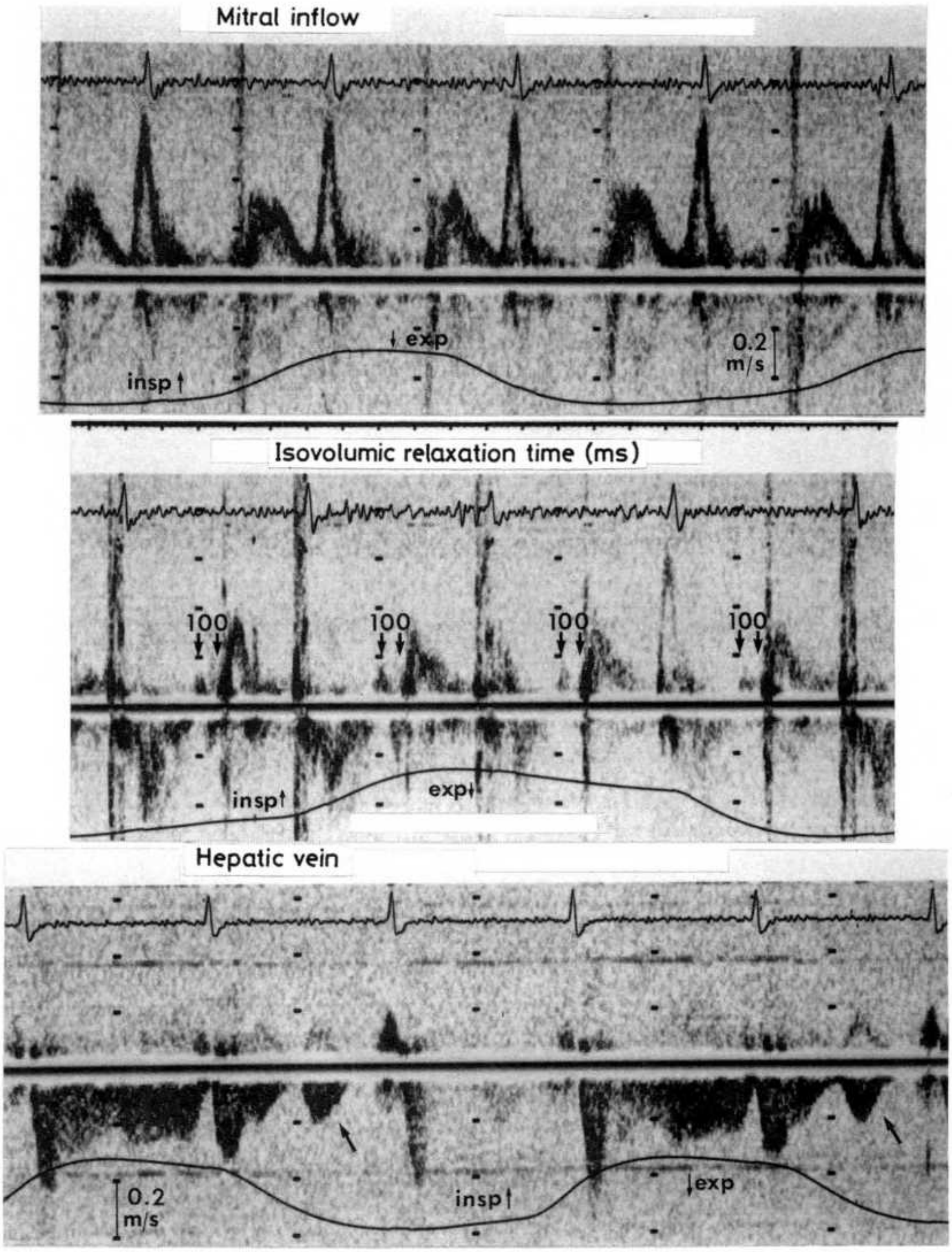

Figure 3 Pulsed wave Doppler findings after pericardiocentesis. Respirometry tracing shows the onset of inspiration (insp) and expiration (exp). There was no appreciable respiratory variation in early mitral inflow velocities. The isovolumic relaxation time (between pairs of arrows) was constant throughout the respiratory cycle. Diastolic hepatic venous filling (arrows) in early expiration was restored.

pulmonary venous filling pressure. In addition, these changes reciprocally interrelate with changes in the right heart where early diastolic filling velocities are increased across the tricuspid valve with inspiration and decreased with expiration.[7] This reciprocal ventricular interdependence is probably the result of respiratory augmentation of venous return in the face of restricted intracardiac volume changes caused by extracardiac compression. Neither the mitral E wave velocity nor the isovolumic relaxation time vary significantly with respiration in patients without tamponade.[7]

Early expiratory decrease or loss of systemic venous diastolic inflow velocities by Doppler has also been detected in tamponade.[7] This finding correlates with the nadir of the tricuspid early inflow velocity, presumably due to maximisation of impedance to right ventricular filling during early expiration.

In our laboratory the same findings were seen in patients with tamponade studied with pulsed wave Doppler and respirometry.[8] These Doppler findings consistently resolve after pericardiocentesis.[7,8]

The diagnosis of "low pressure cardiac tamponade" was confirmed by invasive haemodynamic measurements in this patient. The expanding intrapericardial volume in the setting of hypovolaemia precipitated cardiac tamponade with the diastolic pressure equilibration at low intracardiac pressures and with equilibration of right atrial and intrapericardial pressures. These haemodynamic findings have been described before.[1,9,10]

It has been reported that low pressure tamponade, despite occurring in hypovolumic states, does not respond to volume repletion.[2,9] This was seen in this patient, presumably because of the development of a steep intrapericardial pressure-volume curve, curtailing cardiac filling volume.[9]

Pericardial effusions are common after cardiac surgery but they rarely cause clinical cardiac tamponade.[11] Haemodynamically significant postoperative pericardial effusions, however, can be loculated, small in volume, and often fail to present the usual signs of tamponade on cross sectional echocardiography.[3]

Pulsed wave Doppler echocardiography with respirometry can greatly facilitate the non-invasive diagnosis of cardiac tamponade. As shown by this case, Doppler echocardiography may be particularly useful for the diagnosis of low pressure cardiac tamponade when the clinical examination and even cross sectional echocardiography may be misleading.

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NOTICES

British Cardiac Society

The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts was 19 January 1990.

Cardiac Doppler

The Fifth International Congress of the International Cardiac Doppler Society will take place in Trondheim on 13 to 15 September 1990. Inquiries to Congress Secretariat, The Norwegian Institute of Technology, Department of Continuing Education, N-7034 Trondheim, Norway.

Cardiology and cardiac surgery

A workshop on Update in Cardiology and Cardiac Surgery: East–West Meet will be held at the Institute of Cardio-Vascular Diseases, Madras on 11 to 13 January 1991. Further information from Dr K M Cherian, Institute of Cardio-Vascular Diseases, 180 NSK Salai, Madras – 26, India.

Br Heart J 1990;63.141–3

BRITISH
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Editorial

Electrical neurostimulators for pain relief in angina

The idea that stimulating afferent nerve fibres can relieve pain grew out of Melzack and Wall's gate theory of pain.[1] According to this concept, stimulation of large afferent A fibres (which do not transmit pain) reduces the input to the brain from the peripheral pain receptors via the small myelinated and unmyelinated C fibres. The theory gives a crude explanation for the variability of the sensation of pain. High frequency stimulation with pulse widths of between 100 and 200 μs, which stimulates the large A fibres (but not the C fibres), reduced the sensation of pain.[2] This technique was used with some success to treat chronic pain, initially with external transcutaneous stimulators and more recently with direct spinal cord stimulation via epidural electrodes.[3] In a few patients intermittent claudication was also relieved and indeed many had noted a sensation of warmth in their legs when neurostimulation was applied.[4 5] Further work has confirmed that neurostimulation is useful in severe peripheral vascular disease in relieving pain, healing trophic ulcers, and increasing capillary blood flow and transcutaneous oxygen tension.[5–8] The effects are similar to those of sympathectomy.

Indeed sympathectomy was used to treat angina, and Apthorp *et al* in 1964 found that it relieved angina in about 75% of patients.[9] The use of neurostimulation to relieve angina follows logically from its use in peripheral vascular disease. Its development was cramped, however, by the fact that if pain is inhibited ischaemia will continue unabated. But it is now clear that the relation between angina and ischaemia, as illustrated by the increasing awareness of silent ischaemia, is not constant and painful stimuli may be modified by many factors.[10–13] It is increasingly apparent that neurostimulation is not dangerous and it can help patients who have severe intractable angina despite standard treatment.[14–22]

Techniques and mode of stimulation

In transcutaneous nerve stimulation two large silicon rubber electrodes (connected to a battery powered neurostimulator) are placed over the area of pain and on the other side of the spine in the same dermatome to produce segmental stimulation. Pulse widths of 100–200 μs (and frequency between 75 and 150 Hz) selectively stimulate the large fibres and produce a tingling sensation or parasthesia.

However, transcutaneous nerve stimulation limits the patient's mobility and sensitivity or rashes occur around the electrodes. Therefore, implantable systems have been developed. The epidural electrode (unipolar or bipolar) is inserted through a standard epidural puncture, which is positioned to produce parasthesia in the area of the pain, and is connected to a neurostimulator unit that is implanted in an axillary pouch.

Mechanism of action

The connection between ischaemia and pain is complex and it is not known how neurostimulation influences this. There are several possibilities.

Does neurostimulation increase coronary blood flow? Non-invasive studies suggested that there was less ischaemia in some patients.[14–17 20–22] A recent study from Belgium assessed regional myocardial perfusion by positron emission tomography with potassium-38 as a tracer in seven patients with epidural spinal cord stimulators before and after exercise.[23] There was no significant increase of perfusion to abnormal segments after maximal exercise despite a reduction in angina and an increased time to the onset of ischaemia, although perfusion during stimulation at rest was higher than in the controls. In peripheral vascular disease, however, epidural neurostimulation improved microvascular blood flow.[7 8] It is likely that any changes in perfusion are small, occur mainly in the ischaemic areas, and will be difficult to detect in the heart. Local flow can be adjusted without any increase in total flow, for example the so-called "Robin Hood" effect of aminophylline.[24]

The effects of neurostimulation have been likened to sympathectomy. Although the relief of pain alone may indirectly reduce ischaemia by reducing reflex sympathetic nervous activity, stimulation of the dorsal column may have a direct effect. Currents spread from the dorsal columns into the intermediate columns of the grey area, releasing segmental spinal reflexes that tonically inhibit sympathetic discharge and this may cause vasodilatation. Prostaglandins may be involved too. Hilton and Marshall showed vasodilatation in the cat gastrocnemius muscle after dorsal root stimulation.[25] It was unaffected by sympathetic blocking agents and greatly reduced by prostaglandin inhibitors. They concluded that activity in the afferent fibres of skeletal muscle produces an increase in muscle blood flow mediated by the release of prostaglandins. The same mechanism may be active in the heart.

Direct suppression or inhibition of pain pathways in the spinal cord is one of the most likely mechanisms. Recent experimental work has shown that dorsal column stimulation inhibits activity of spinothalamic tract cells evoked by the electrical stimulation of cardiopulmonary sympathectic afferents and by intracardiac bradykinin.[26] Thus it is likely that dorsal column stimulation directly inhibits the transmission of nocioceptive cardiac stimuli and thus lessens the sensation of pain.

Another mechanism for pain suppression is stimulation of endogenous opiates. Low frequency electroacupuncture has been shown to cause a rise in concentrations of β endorphin (but not met-enkephalin) in the cerebrospinal fluid in association with relief of pain.[27] Naloxone can reverse the effect of acupuncture.[28] In patients with exercise induced myocardial ischaemia, plasma concentrations of endorphin are increased with exercise, and concentrations after exercise are related to the time to onset of angina and it is possible that endorphins may alter the perception of pain caused by myocardial ischaemia.[29] It has been suggested that transcutaneous nerve stimulation and epidural spinal electrical stimulation can increase concentrations of β endorphin. However, Mannheimer and his colleagues showed that naloxone, which is a pure opiate antagonist, does not abolish the effect of transcutaneous nerve stimulation.[17] Electroacupuncture, however, usually uses low frequency stimulation which increases β endorphins which can be antagonised by naloxone, whereas the high frequency stimulation used with transcutaneous nerve stimulation may release met-enkephalins which are not blocked entirely by conventional doses of naloxone. Opiate peptides may be involved in modulating sympathetic activity within the heart (which has opiate receptors) especially during stress, pain, or hypoxia.[28-30] Until more specific agonists and antagonists are available to probe the action of opioid peptides, any possible action of neurostimulation via endorphins remains mere speculation.

Clinical results in patients with angina

The clinical use of epidural neurostimulation for patients with angina is limited. Assessment of these techniques is difficult because the treatment of painful conditions is especially susceptible to the placebo effect. But sham studies or double blind placebo controlled trials are impossible with neurostimulators because the patient feels parasthesia and the electrical activity interferes with electrocardiographic recordings. The use of transcutaneous nerve stimulation in the treatment of angina patients has been studied in depth by Mannheimer and his colleagues.[14-17] They showed that treatment with transcutaneous nerve stimulation reduces pain, increases tolerance to pacing, improves lactate metabolism, and is associated with less pronounced ST segment depression. In long term studies the group treated with transcutaneous nerve stimulation had increased work capacity (as assessed by repeated bicycle ergometry tests), reduced frequency of angina attacks, and reduced consumption of nitrates compared with an untreated control group. We found that transcutaneous nerve stimulation was useful for the control of severe angina and rest pain in patients who were not candidates for operation. The effect was often impressive.

The first report of epidural neurostimulation for the relief of angina was that of Murphy and Giles from Perth, Australia.[18] They described relief of angina after implantation in a 54 year old woman with a long history of angina. In a later report Murphy and Giles described another 10 patients who had good clinical benefit.[19] Mannheimer and his colleagues reported on a further 10 patients,[20] confirming the considerable clinical improvement that was associated with an increase of working capacity and time to angina, less ST segment depression, and a shortened recovery time. Our results in 11 patients were promising.[21 22] We did not abolish angina in all patients but in some the improvement was remarkable, with a significant drop in consumption of glyceryl trinitrate. Some have returned to work. Treadmill exercise testing showed an increase in exercise duration and some lessening of ST segment depression at comparable work loads. None the less, there does not seem to be any close relation between symptomatic improvement and reduction of ischaemia on exercise testing or right atrial pacing and there seems to be a mixture of pain relief and reduction of ischaemia. The beneficial effects have persisted for more than a year and to date we have no evidence that mortality is increased; however, the numbers treated remain small. The prolonged improvement argues against any placebo effect, especially in these patients who often had a rapid recurrence of pain after coronary artery bypass grafting.

It seems that both transcutaneous nerve stimulation and epidural spinal electrical stimulation are useful techniques for the relief of angina. Pain may be inhibited both centrally in the spinal cord and peripherally in the heart and the relief of pain may lessen ischaemia by a reduction of sympathetic nervous activity. The effect of neurostimulation is sometimes so considerable that factors other than mere pain relief must be involved, such as a redistribution of local blood flow to ischaemic areas as occurs in patients with peripheral vascular disease. Neurostimulation is not therefore an eccentric offshoot of acupuncture but is likely to become a useful treatment. Furthermore, discovering how it works may clarify the complex mechanisms of ischaemic pain.

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Editorial

Cardiac defects in the children of mothers with high concentrations of plasma phenylalanine

Postnatal brain damage in a homozygous affected child with phenylketonuria is well recognised. Less well known, despite its recognition over thirty years ago[1], is the damage that even a heterozygous fetus can incur in a homozygous mother with high blood concentrations of phenylalanine. Low birth weight, microcephaly, mental retardation, and congenital heart disease are most often seen but other defects of structure have been reported. Lenke and Levy in their retrospective survey found congenital heart disease in 12–15% of the offspring of untreated mothers with classic phenylketonuria.[2] Typically these women had phenylalanine concentrations in excess of 1200 μmol/l, more than 15 times the normal value. Because the placenta transports amino acids actively, fetal blood concentrations are higher than those in the mother—with the ratio of fetus to mother for phenylalanine being around 1·6. There is evidence too that high maternal phenylalanine values may decrease the transfer of some other amino acids across the placenta[3] so that the fetus may have immensely high concentrations of phenylalanine but be relatively deficient in some other amino acids. Similarly, in animals there is evidence that high fetal blood concentrations of phenylalanine may interfere with the transport of other amino acids through the blood brain barrier into the central nervous system.[4] Poor fetal growth, low birth weight, microcephaly, and mental retardation may all be ascribed to the resulting amino acid imbalances quite apart from other possible toxic effects of phenylalanine or its metabolites.

The sensitivity of the postnatal brain to high concentrations of phenylalanine has been known for decades. Congenital heart disease, however, is different. The congenital cardiac abnormalities are classic defects of organogenesis that can be traced back to the fifth to eighth weeks of fetal life during which the heart develops from a simple tube into a four chambered structure with separate atrioventricular canals and separate outflow tracts developing from the common truncus arteriosus. The congenital defects in maternal phenylketonuria have included coarctation of the aorta, hypoplastic left ventricle, mitral valve atresia, ventricular septal defects, Fallot's tetralogy,[5] and now, as reported on page 180 of this issue, an anomalous coronary artery.[6] There are some major unanswered questions. For example, is any particular pattern of congenital cardiac defects commoner in maternal phenylketonuria? Why should the heart apparently be the next most vulnerable organ in the fetus after the central nervous system? The incidence of mental retardation in untreated maternal phenylketonuria when the mother's phenylalanine exceeds 1200 μmol/l is around 90% and the incidence of microcephaly only slightly less. These incidences are much higher than that of congenital heart disease but the question of unexpected cardiac susceptibility remains.

One theory relates to a link between the developing central nervous system and the embryonic heart. Kirby and Miyagawa have drawn attention to the evidence that neural crest cells are important for normal cardiac development.[7] The neural crest cells migrate away from the neural plate as it closes to form the neural tube. Incidentally, a higher incidence of neural tube abnormalities has not yet been reported in the offspring of mothers with phenylketonuria. Cranial neural crest cells move during normal embryonic development into the pharyngeal arches and pharyngeal region. Some of these, the cardiac neural crest cells, have been identified in association with the aortic arch arteries and the developing outflow tract. Studies of neural crest ablation in developing chick embryos produced various cardiac anomalies and it seems that migrating neural crest cells are critical in the control of cardiac development. Could congenital cardiac damage in maternal phenylketonuria ultimately be the result of another adverse effect on cells of neural plate origin—in addition to the adverse effects on the same tissue that lead to microcephaly and mental retardation? Unifying hypotheses are always attractive. Proof is more difficult. Other defects of organogenesis—such as oesophageal atresia—have been described in the offspring of mothers with phenylketonuria[2] but whether these can be linked to an adverse effect on neural crest cells has not been suggested and indeed it is not clear whether these defects are truly more common than in the normal population. Proof that maternal phenylalanine in some way adversely affects the fetal heart through an effect on neural crest cells will need experimental work in animals that closely models the human biochemical defect. Work on that has started.

Whatever the theoretical aspects of the problem some practical issues are already clear. Naughten and Saul reported three deaths in infancy in their series of 50 offspring born to mothers with phenylketonuria, two of which were caused by congenital heart disease.[8] I know of two deaths from congenital heart disease in a series of only 12 offspring. It is a serious problem which cannot be prevented unless the mother's blood concentration of phenylalanine is lowered before the start of cardiac development. It is too late to start dietary measures when a woman is 7 weeks pregnant.[9,10] In practice this means a pre-conception diet and a planned pregnancy when the mother's phenylalanine is low. The deaths referred to above all occurred when a strict diet was started after conception. There is already evidence that a pre-conception diet lowers the incidence of congenital heart disease. Lenke and Levy[2] found no cases of congenital heart disease in 44 offspring of mothers with phenylalanine values below 600 μmol/l and Drogari *et al* found no examples of congenital heart disease in 17 offspring after a strict diet had been started before conception.[11]

For the cardiologist there is great theoretical interest in the mechanisms of congenital heart disease, and maternal phenylketonuria may offer unique insights into such problems. From a practical point of view is it worth screening all mothers of children with congenital heart disease for maternal phenylketonuria? This depends on whether undiagnosed maternal phenylketonuria exists in the population. Before the advent of widespread neonatal screening around 1970–1972 cases of phenylketonuria were definitely missed. Most of these individuals became intellectually impaired as a result; so mothers of low IQ who have a child with congenital heart disease should be tested for phenylketonuria. A small number of women in whom phenylketonuria was not diagnosed in early life did achieve IQ values in the normal range.[12] For this reason if a child has both congenital heart disease and other suggestive clinical features such as microcephaly or low IQ it is worth testing the mother for phenylketonuria regardless of her IQ. Finally, because it is clear that the risk of damage extends to all offspring of a mother with phenylketonuria if it is untreated by diet any mother with more than one child with congenital heart disease must be tested for raised plasma phenylalanine.

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ORIGINAL ARTICLES

Identification of a high risk subgroup of patients with silent ischaemia after myocardial infarction: a group for early therapeutic revascularisation?

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Abstract

Asymptomatic ("silent") ischaemia has been shown to be of prognostic significance in patients with stable and unstable angina and more recently in patients recovering after myocardial infarction. No therapeutic regimen has yet been shown to improve the prognosis of patients with silent ischaemia after infarction, which can be found in as many as a third of these patients. Attempts to achieve therapeutic revascularisation in all these patients may be undesirable, but early revascularisation could be especially beneficial in some selected high risk patients. Two hundred and fifty consecutive clinically stable survivors of myocardial infarction who had pre-discharge submaximal exercise tests were followed up for a year. Silent ischaemia was found in 27% of these patients; 15% had symptomatic ischaemia. Patients with a positive exercise test were prescribed a β blocker before discharge. Mortality in patients with silent (9·4%) and symptomatic (5·4%) ischaemia in the first year after infarction was not significantly different. Patients with symptomatic ischaemia were more likely to have undergone coronary artery bypass grafting in the first year. Patients with silent ischaemia were, however, significantly more likely to die than patients with a negative exercise test (relative odds 12:1). Patients with silent ischaemia and an abnormal blood pressure response or who could not complete a submaximal exercise protocol were at particularly high risk, being 32 times more likely to die than those with a negative test (95% confidence interval from 3·3 to 307 times more likely). First year mortality in this group was 22%. The benefits of therapeutic revascularisation in this high risk group need to be studied.

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Silent ischaemia has been recognised since early this century ("angina sine dolore").[1] It occurs when there is objective evidence of myocardial ischaemia without symptoms. Such evidence is usually the presence of ST segment changes, detected during either exercise[2-4] or ambulatory electrocardiograms,[5-7] or abnormalities seen during thallium scintigraphy.[8 9] Silent ischaemia has been studied in patients with stable and unstable angina[10-12] and, more recently, in selected patients after myocardial infarction.[8 13 14] These studies suggested that silent ischaemia after infarction is associated with an adverse prognosis and is detectable in as many as a third of patients after infarction. Many patients who die in the first year do so suddenly. Evidence in growing that sudden death after infarction is related to a new ischaemic event more often than has been realised.[15] Therapeutic revascularisation of all patients with evidence of ischaemia soon after infarction may improve the survival of this group, but this would make enormous demands on currently available services and may be undesirable for patients at lower risk. We therefore undertook this study to see whether we could identify a group of patients with silent ischaemia who were at particularly high risk and who might benefit from early attempts at revascularisation. We studied only those who were clinically stable seven days after an infarct, because those with complicated early courses had already identified themselves as being at higher risk; the clinical and angiographic characteristics of these patients were reported elsewhere.[16]

Patients and methods

We studied 302 (254 (84%) male and 48 (16%) female; mean (SD) age 54 (7·3) years) consecutive patients aged ⩽65 who were clinically stable seven days after myocardial infarction. We used conventional criteria to diagnose Q wave and non-Q wave myocardial infarction and define anterior and inferior infarction.[16] Forty patients were excluded: 10 who were unable to perform the exercise test, four with left bundle branch block, four patients with other medical conditions that carried an adverse prognosis, one patient in whom unstable angina developed during the first 7 days, one patient with previous coronary artery surgery, one patient in whom atrial flutter developed on the exercise test, and 19 patients who were not given an exercise test because of administrative error. An early submaximal exercise test was therefore undertaken by 262 patients. No β blockers had been prescribed for 36 hours and digoxin had been stopped at least 7 days before the exercise test.

EXERCISE TEST PROTOCOL

Patients were exercised using the second and third stages of the modified Bruce protocol. The median interval from infarction to the exercise test was 11 days (interquartile range 9–12). Cuff systolic blood pressure measurements and a 12 lead electrocardiogram were recorded before the test, at the end of each 3-minute stage; and 2, 5, and 10 minutes into the recovery phase. The test was stopped early if there was severe angina pectoris, severe dyspnoea, fatigue or ataxia, ST depression $\geqslant 5$ mm 80 ms after the J point, or increased ventricular extrasystoles ($\geqslant 10$/min or triplets). Predetermined criteria were set to define "positive" and "negative" tests: (*a*) development of angina pectoris; (*b*) development of horizontal or down-sloping ST depression $\geqslant 1$ mm, 80 ms after the J point; (*c*) inappropriate blood pressure response defined as failure of the systolic blood pressure to rise by $\geqslant 10$ mm Hg—or having risen, to fall again by $\geqslant 10$ mm Hg; (*d*) inability to complete the exercise test because of severe dyspnoea, fatigue, or ataxia; and (*e*) development of a ventricular extrasystolic rate that was $\geqslant 6$ beats higher than the count on the resting pre-exercise electrocardiogram, or the development of ventricular triplets.

GROUP UNDERGOING CARDIAC CATHETERISATION

Cardiac catheterisation was performed on 123 of 139 patients with a positive exercise test at a median of 21 (interquartile range 16–31) days after infarction. The remaining 16 did not undergo catheterisation: because of early death (four), refusal (five), incorrect reporting of the exercise test as negative (four)—in each case an inappropriate blood pressure response had been overlooked, or administrative error (three). During cardiac catheterisation we measured several variables[16]; these included a left ventricular regional wall motion score based on that of the Coronary Artery Surgery Study,[17] the number of vessels with a stenosis of >50% of the diameter, an overall coronary artery score (a high score reflecting more extensive disease), and a score to reflect the supply of collateral vessels to the infarct territory.

FOLLOW UP

Patients with a positive exercise test were all prescribed a β blocker (sotalol) (unless contraindicated) 1–2 days before discharge in a dose sufficient to reduce the resting heart rate to $\leqslant 60$ beats/min. The development of angina was treated with the addition of nitrates or calcium channel blockers, and coronary artery surgery was offered for angina not controlled with medication or if we believed that this would improve the prognosis based on arteriographic criteria.[18, 19] Treatment for the "negative" group was not standardised. Follow up data were collected for one year after infarction. Of the 262 patients who performed the exercise test, 16 were lost to follow up: six from the positive group and 10 from the negative group. Six of the exercise tests could not be analysed because the recordings were lost; of these, five had been reported as negative and one as positive. Follow up on these six was complete. There were thus 240 patients with interpretable exercise tests and complete follow up. Of the 16 patients lost to follow up, six also had missing exercise tests at the time of analysis. There were, therefore, 250 well-documented exercise tests.

STATISTICAL ANALYSIS

Data were analysed with the SPSS/PC+ program on a Sperry PC/IT computer. Unordered categorical variables were compared by χ^2 analysis with Yates's correction as appropriate. Means were compared by analysis of variance. Likelihood ratios were calculated where appropriate.[20]

Results

INCIDENCE AND INTERRELATIONS OF ST SEGMENT DEPRESSION AND ANGINA (TABLE 1)

Of the 104 patients in whom ST segment depression developed, 67 (64%) had no symptoms while angina developed in 37 (36%). Those with silent ischaemia accounted for 27% of the 250 patients with well-documented exercise tests after infarction. Forty six (18%) had ST segment depression as the only abnormality on exercise. Twenty three patients had a positive exercise test on the basis of criteria other than those used to identify these groups. A total of 123 patients had negative tests.

CLINICAL OUTCOME (TABLES 2 AND 3)

Six patients with silent ischaemia died—three suddenly, one after further myocardial infarction, and one in intractable heart failure; the circumstances surrounding the death of the sixth patient were not known (table 2). Two patients with angina and one patient with a negative exercise test died suddenly. The first year mortality of the patients excluded from the exercise protocol was 19% and that of the patients with positive exercise tests on criteria other than angina or ST depression was 26% (six patients).

Patients with silent ischaemia were 12 times more likely to die in the first year than patients with a negative exercise test (p = 0·005) (95% confidence intervals from two to 65 times more likely to die) (table 3). They were nearly twice as likely to die as those with angina, though the difference was not statistically significant (95% confidence interval for the difference between the two groups from 6% better in the group with silent ischaemia to 14% better in the group with angina). Patients with angina were,

Table 1 Patient study groups

Groups	*Silent (n = 67)*	*Symptomatic (n = 37)*	*Negative (n = 123)*
Angina	–	+	–
ST segment depression	+	+	–

Table 2 Characteristics of patients with silent ischaemia who died

Case	Sex	Age	Risk factors	Prev MI	Infarct site	Q or non-Q wave	Other exercise test features	Angiographic features: LV score	CA score	No. VD	Colls	Mode/time of death
1	M	56	DM	–	Anterior	Q	Abnormal BP response, ECG recovery >5 min	30	35	4	3	MI/10 mnth
2	M	61	Smoker	–	Anterior	Q	Test (6 min) not completed, ST segment elevation, 5 mm ST depression, ECG recovery >5 min	33	22	1	2	SD/5 mnth
3	M	56	Smoker, HT, DM	–	Inferior	Non-Q	Resting ST segment depression 0·1 mV, ECG recovery 2–5 min	25 An	28	2	0	CCF/2 mnth
4	M	55	Smoker, FH	–	Inferior	Q	Resting ST segment depression 0·1 mV, ST segment elevation, ECG recovery 2–5 min	22	16	2	0	SD/9 mnth
5	M	46	Smoker	–	Inferior	Non-Q	Abnormal BP response, ECG recovery >5 min	21	38	4	4	Unknown/ 1 mnth
6	M	60	Smoker, FH	+	Anterior	Q	Test (6 min) not completed, ST segment elevation, ECG recovery >5 min	26	18	2	3	SD/2 mnth

An, aneurysm, BP, blood pressure, CA, coronary artery, CCF, congestive cardiac failure; Colls, collateral score; DM, diabetes mellitus, ECG recovery time, time taken for ST segment depression developing during exercise to return to level of resting ECG before test; FH, positive family history; HT, hypertension, LV, left ventricular; MI, myocardial infarction, SD, sudden death, ST segment elevation, elevation in leads reflecting infarct, VD, vessels diseased.

however, more likely to have undergone coronary artery bypass surgery (30% *v* 14% of those with silent ischaemia ($p = 0·06$)), probably because they were more likely to have complained of angina in the first year after infarction (79% *v* 41%, $p < 0·005$).

To refine the risk stratification of patients with silent ischaemia they were separated into two subgroups—those with and those without at least one of the other criteria that had been used to define a positive exercise test. Four of the six patients who died in the first year had shown an additional feature (an abnormal blood pressure response, patients 1 and 5; or an inability to complete the submaximal protocol, patients 2 and 6) (table 2). A high risk group of patients with silent ischaemia was thus identified (table 4); these patients were more likely to die than any of the other groups. The "high-risk" patients with silent ischaemia were not only 32 times more likely to die than the patients with negative exercise tests (95% confidence interval from 3·3 to 307 times more likely), but they were 6·5 times more likely to die than the "low risk" patients with silent ischaemia (95% confidence interval from 1·2 to 33 times more likely), and five times more likely to die than those with symptomatic ischaemia (95% confidence interval from 0·9 to 27 times as likely).

SUBGROUP ANALYSES:ALLOWANCE FOR "RECIPROCAL" CHANGES

In some patients the development of ST depression might have been a reciprocal change in response to the development of ST elevation in the infarct territory on exercise. In two studies of post-infarct patients this feature typified a group with extensive left ventricular damage.[21 22] This factor may account for the increased mortality in the group with silent ischaemia (as well as the group with symptoms) compared with those with a negative test. We performed further analyses to investigate this possibility. These showed that the increased mortality was not confined to those with ST segment elevation; this applied for all patients with ST depression, whether this was silent or symptomatic. Of the 67 patients with silent ischaemia, 28 developed ST segment elevation in the territory and three (11%) died in the first year. Of the 39 patients without ST elevation, three (7·7%) died.

Table 3 Clinical outcome in the first year after infarction in patients with silent and symptomatic ST depression

	Silent (n = 64*)	Symptomatic (n = 37)	Negative (n = 113*)
Dead (no, %)	6 (9·4)	2 (5·4)	1 (0·9)
Relative odds	12	6·4	1
Angina (no, %)	26 (41)	29 (79)	31 (27)
Relative odds	1·7	9·6	1
Coronary artery bypass grafting (no, %)	9 (14)	11 (30)	3 (2·7)
Relative odds	5·7	16	1
Myocardial infarction (no, %)	3 (4·7)	1 (2·7)	3 (2·7)
Relative odds	1·7	1	1
Left ventricular failure (no, %)	5 (7·8)	1 (2·7)	3 (2·7)
Relative odds	3	1	1

*Some lost to follow up

COMPARISON OF CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF PATIENT GROUPS (TABLE 5)

We compared the clinical features in all the groups and the exercise responses and angiographic features in the groups with silent ischaemia and angina.

History and 12 lead electrocardiogram (table 5)

The only significant difference between the groups was that 25% of patients with silent ischaemia had a history of hypertension compared with 11% of those with a negative test ($p = 0·008$). Of the total number of patients with a history of hypertension, 34% had a resting ST segment change of $\geq 0·05$ mV compared with 17% of those who did not have hypertension ($p < 0·02$). Of all patients with resting ST segment depression $\geq 0·05$ mV, 72% developed at least 0·1 mV of further ST segment depression on exercise compared with 32% of those without resting changes ($p < 0·001$).

There was no difference in the distribution of sites of infarction between patients with silent ischaemia and symptomatic ischaemia, but those with silent ischaemia were more likely to have had an inferior infarct than those with a negative exercise test (63% *v* 43%, $p = 0·01$). Patients with symptomatic ischaemia were more likely (57%) than both the silent (34%) and the negative (28%) test groups to have had a non-Q wave infarction.

Table 4 Silent ischaemia: a high risk subgroup

	Silent ischaemia (higher risk) (18)		*Silent ischaemia (lower risk) (46)*		*Symptomatic ischaemia (37)*		*Negative exercise test (113)*	
Dead at 1 year								
(no, %)	4	(22)	2	(4 3)	2	(5 4)	1	(0 9)
Relative odds	32		5 1		6 4		1	
CABG *(no, %)	4	(22)	5	(11)	11	(30)	3	(2 7)
Relative odds	10		4 5		16		1	

*No patient undergoing coronary artery bypass grafting (CABG) died in the first year.
Three patients were lost to follow up

Other exercise test variables (table 5)

Patients with symptomatic ST depression were less likely to complete the submaximal exercise test than patients with silent ischaemia. There were no significant differences in the distribution of the other exercise test variables. The absence of symptoms in the group with silent ischaemia could not be accounted for by a slower heart rate nor a different acceleration of heart rate nor by a lower double product.

Angiographic variables (table 5)

The groups with silent ischaemia and a negative test could not be distinguished by differences in the degree of left ventricular damage, number of vessels diseased, extent of coronary disease, or the degree of collateralisation.

Discussion

Silent ischaemia is of prognostic relevance in patients with asymptomatic,[23 24] stable,[25 26] or unstable coronary artery disease.[27–29] Its importance after infarction is less clear. We found silent ischaemia, identified by means of a predischarge exercise test, in 27% of clinically stable patients after myocardial infarction. This accords with two other major studies: in one, silent ischaemia was identified in 23% of patients by means of an exercise test,[8] and in the other ambulatory ST segment monitoring showed silent ischaemia in 29% of a higher risk group.[14] We do not know, however, whether currently available therapeutic options can improve the prognosis of patients with silent ischaemia, whether or not this follows infarction.[30]

In our study, mortality was higher in patients with silent ischaemia than in those with a negative exercise test. The fact that patients with a positive exercise test were treated with a β blocker before discharge but patients with a negative test were treated at the discretion of their referring physician is not likely to have confounded these results. It is unlikely that this treatment harmed the group with a positive exercise test because these drugs improve prog-

Table 5 Differences in clinical, ECG exercise test, and angiographic variables between groups

	Silent (n = 67)		*Symptomatic (n = 37)*		*Negative (n = 123)*		*Statistical analysis**		
	No	*(%)*	*No*	*(%)*	*No*	*(%)*	*Silent v symptomatic*	*Silent v negative*	*Symptomatic v negative*
History									
Male	58	(87)	30	(81)	110	(89)	NS	NS	NS
Female	9	(13)	7	(19)	13	(11)			
Previous MI	6	(9)	5	(14)	4	(3)	NS	NS	NS
Smoker	58	(87)	30	(81)	94	(76)	NS	NS	NS
Diabetes	11	(16)	3	(8)	12	(10)	NS	NS	NS
Hypertension	17	(25)	6	(16)	13	(11)	NS	p = 0 008	NS
+ ve Family history	17	(25)	9	(24)	24	(20)	NS	NS	NS
Site/type of MI·									
Anterior†	23	(34)	15	(41)	65	(53)	NS	p = 0 01	NS
Inferior†	42	(63)	21	(57)	53	(43)			
Q wave	44	(66)	16	(43)	89	(72)	p = 0 03	NS	p = 0 001
Non-Q wave	23	(34)	21	(57)	34	(28)			
Positive exercise test variables.									
Inability to complete	4	(6)	7	(19)			p = 0 04		
Abnormal BP response	14	(21)	12	(32)			NS		
Ventricular arrhythmias	4	(6)	3	(8)			NS		
ST elevation	28	(42)	12	(32)			NS		
Mets when ST depression occurred.									
≤3	40	(60)	18	(49)			NS		
4–5	27	(40)	19	(51)			NS		
≤2 mm of ST depression	55	(82)	34	(92)			NS		
>2 mm of ST depression	12	(18)	3	(8)			NS		
<2 min ECG recovery time	7	(10)	4	(11)					
2–5 min ECG recovery time	27	(40)	17	(47)			NS		
>5 min ECG recovery time	33	(49)	15	(41)					
Mean heart rate at rest (SD)	78	(18)	73	(13)			NS		
Mean heart rate at 3 min (SD)	112	(21)	109	(25)			NS		
Mean heart rate at 6 min (SD)	120	(22)	116	(18)			NS		
Mean rate diff 3 min − rest (SD)	34	(12)	37	(22)			NS		
Mean rate diff 6 min − rest (SD)	43	(13)	44	(17)			NS		
Angiographic variables‡									
0 vessels diseased	1	(1 6)	1	(2 9)					
1 vessel diseased	19	(30)	5	(15)					
2 vessels diseased	18	(28)	12	(35)			NS		
3 vessels diseased	16	(25)	12	(35)					
4 vessels diseased	10	(16)	4	(12)					
Mean coronary artery score (SD)	21	(8 4)	23	(8 8)			NS		
Mean left ventricular score (SD)	21	(5 8)	19	(5 8)			NS		
Mean collateral score (SD)	2 56	(1 56)	2 97	(1 55)			NS		
Collateral score groups									
None (score 0)	13	(20)	6	(18)			NS		
Minor (score 1, 2)	11	(17)	2	(5 9)			NS		
Major (score 3, 4)	40	(63)	26	(77)			NS		

*χ^2, but analysis of variance for means only $p < 0\ 05$ shown, NS, not significant.
†Excluding those with new infarction in both territories
‡Patients with positive exercise rest.
Mets, metabolic equivalents.

nosis after infarction[31] and were not prescribed if there were contraindications. Mortality in patients with silent ischaemia (9·4%) and symptomatic ischaemia (5·4%) was not significantly different. Those with symptomatic ischaemia were more likely to undergo coronary artery bypass grafting—probably because they were more likely to have angina in the year after infarction. None of the patients undergoing operation died within the first year. Although it has never been formally tested in post-infarct patients, careful selection of patients for early revascularisation is likely to improve prognosis.[32] Our results indicate that the absence of symptoms associated with silent ischaemia should not necessarily preclude patients from a revascularisation programme. Attempted revascularisation of all patients with silent ischaemia after infarction is, however, probably not desirable.[33-35] A group of patients with silent ischaemia who were at particularly high risk was identified by ST segment depression during exercise accompanied by an abnormal blood pressure response or by the patient's inability to complete the submaximal exercise protocol. Mortality was 22% in this group. Although by no means forming a comparable group, the patients receiving placebo in the Coronary Drug Project (men who had survived to at least three months after infarction) had a first year mortality of about 5%. Only those in the top three deciles of risk (based on 10 clinical characteristics) had a *five year* mortality greater than 22%.[36] The benefit of therapeutic revascularisation in these patients should be studied in a much larger population. Our findings suggest that objective evidence of ischaemia after infarction should lead to further stratification and not simply be considered as a concept to "excite and reward underemployed cardiologists".[37]

The coronary arteriographic characteristics of the groups with silent ischaemia and symptomatic ischaemia were similar—indicating that symptoms are not caused by more widespread coronary disease, and confirming similar observations made by others.[24 38 39] The extent of left ventricular damage was also similar in the two groups and this factor does not account for the different mortalities. In the Coronary Artery Surgery Study, although patients with both angina and ST depression were somewhat more likely to have triple vessel disease than those with only one of these features, the long term outcome was similar in these three groups; outcome in each group was related to the number of diseased vessels.[24] There are, however, major population differences between such a study and the present one in which only post-infarction patients were investigated.

No features of the previous clinical history helped to distinguish between those with silent ischaemia and those with symptomatic ischaemia. Patients with silent ischaemia, were, however, more likely to have a history of hypertension than patients with a negative exercise test. This difference may be partly explained by a higher incidence of abnormalities on the resting electrocardiogram in patients with a history of hypertension. In such patients further significant ST segment depression on exercise may simply represent an exercise induced exaggeration of an abnormality that is already present. Alternatively, these changes may indicate true ischaemia, reflecting patterns of coronary disease of small vessels or increased oxygen demands in hypertensive patients. An association between hypertension and the development of silent myocardial infarction has been noted before.[40 41] The group with silent ischaemia had a higher incidence of inferior infarction than either the symptomatic group or those with a negative exercise test. Since the 12 lead electrocardiographic exercise test is more sensitive for anterior than inferior ST segment depression,[38] it may be that some patients with anterior infarcts but with residual inferior ischaemia are "missed" by the exercise test when ST segment depression is the only feature considered. Patients with symptomatic ischaemia were more likely to have had a non-Q wave infarction than those with silent ischaemia (relative odds 2·5:1) and patients with negative exercise tests were the least likely to have had a non-Q wave infarction.

There are particular difficulties in defining "ischaemia" on the exercise electrocardiogram soon after infarction. ST segment elevation in the territory of the infarct may become more pronounced on exercise, and if ST segment depression occurs in the electrocardiographic leads that represent the area opposite to this territory, it is impossible to be certain whether this is a reciprocal electrical event or represents true ischaemia. This is potentially important in the context of this study because the group with ST segment elevation might have a higher mortality related to more extensive left ventricular damage. Further analysis, however, showed that mortality was the same whether ST depression occurred alone or together with ST elevation. In addition, it might be argued that patients in whom dyspnoea develops in the presence of ST depression do not have "silent" ischaemia. But there are difficulties in objectively assessing the cause of dyspnoea in patients soon after infarction, and there are advantages in a simple definition of silent ischaemia that allows for comparison between studies.

Exercise testing after myocardial infarction is now recognised as a powerful means of risk stratification; it provides multiple variables some of which are more useful for predicting clinical outcome than others.[16] We found that those with ST depression, whether silent or not, have a higher mortality than those with a negative exercise test. Those patients in whom silent ischaemia is associated with an abnormal blood pressure response or who are unable to complete a submaximal protocol are at particular risk. Patients with symptoms of angina associated with the ST depression are currently more likely to undergo attempted revascularisation than those with silent ischaemia. Our results suggest that withholding therapeutic revascularisation from those with silent ischaemia, particularly the subgroups at higher risk, may be inappropriate. A study is needed to investigate the potential benefit of therapeutic revascularisation in high risk groups.

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Non Q wave infarction: exercise test characteristics, coronary anatomy, and prognosis

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Abstract

The exercise test characteristics, coronary anatomy, and prognosis of patients discharged after non Q wave myocardial infarction were compared with those in whom Q wave infarction occurred. Of the 339 patients studied, all of whom were $\leqslant 70$ years, 87 (26%) had had a non Q wave infarction. There were no significant differences in the exercise test characteristics between the two groups, and in those 149 patients in whom angiography was performed triple vessel disease was present in 36/114 (32%) of the Q wave group and 9/35 (26%) of the non Q wave group. The infarct related artery was more often patent in the non Q wave group (27/35 (77%)) than in the Q wave group (53/114 (46%)). The one year mortality and the reinfarction and angina rates were similar in the two groups and the exercise test remained a good discriminator for predicting patients at risk of future cardiac events in both groups.

In view of the similar outcome and severity of coronary disease in those aged $\leqslant 70$ with non Q wave infarcts, the distinction between Q and non Q wave infarction need not influence management decisions in patients after myocardial infarction.

The short term prognosis for patients with a non Q wave myocardial infarction is excellent[1] with an in hospital mortality of approximately 2%.[2 3] However, recent reports have suggested that patients sustaining a non Q wave infarct may be at a higher risk of late complications—death,[4] reinfarction,[5] and angina[2]—than those with a Q wave infarction. After myocardial infarction, early exercise testing has been shown to be of value in predicting patients at risk from future cardiac events[6-8] and thus might be useful in identifying which patients with non Q wave infarction are likely to benefit from appropriately timed intervention. This study was performed to investigate and compare the exercise test characteristics, coronary anatomy, and prognosis of patients after non Q wave infarction and after Q wave infarction.

Patients and methods

We studied 339 patients aged 34–70 who were able to perform a predischarge exercise test after a confirmed myocardial infarction. No patient had been treated by thrombolysis. Myocardial infarction was defined as the presence of at least two of the following features: (*a*) typical history of ischaemic pain, (*b*) a serum concentration of aspartate transaminase of at least twice normal, (*c*) development of new Q waves (with a duration of at least 0·04 s) or persistent ST/T wave changes.

After the exercise test all patients were put on β blockers before discharge (unless contraindicated) and this treatment was continued for at least one year. During that time full follow up was maintained and the cardiac events of death, reinfarction, and angina were recorded. Coronary artery bypass surgery was only undertaken in those patients whose symptoms were not controlled by medical treatment.

EXERCISE TESTS

Submaximal exercise tests (modified Naughton protocol) were performed in the immediate predischarge period on a treadmill (Medtronics IMC model 210). Blood pressure and 12 lead electrocardiogram (Siemens-Elema Mingocard 7) were recorded while patients were supine and erect before exercise, every 3 minutes during exercise, and at the end of the test. Continuous electrocardiographic monitoring, displayed on an oscilloscope, was performed throughout the test.

Tests were stopped if angina developed or if one of the following pre-defined criteria occurred: (*a*) attainment of 85% of maximum predicted heart rate, (*b*) development of > 0·4 mV horizontal ST segment depression, (*c*) occurrence of complex ventricular arrhythmias, (*d*) exercise hypotension: defined as a > 10 mm Hg fall in systolic blood pressure from the previous reading, (*e*) completion of the 18 minute protocol.

Exercise tests were defined as positive if downsloping or horizontal ST segment depression $\geqslant$ 0·1 mV, measured 80 ms after the J point, occurred during exercise. Positive tests were further designated as "silent" if no angina occurred and as "painful" if they were accompanied by angina. The final double product achieved was the product of the systolic blood pressure and heart rate at maximal exercise.

CORONARY ANGIOGRAPHY

Cardiac catheterisation was performed from either the femoral or brachial approach within three months of infarction. Selective coronary angiography was undertaken and angiograms were recorded in multiple views to allow adequate visualisation of the entire coronary tree. The coronary vasculature was divided into three main trunks: left anterior descending artery, circumflex artery, and right coronary artery. Each trunk was examined for the presence of important disease, which was considered to be present if the luminal diameter of a vessel was reduced by $\geqslant 75\%$. This criterion was used to classify single, double, or triple vessel disease. In addition, the infarct related artery was identified in each patient from the admission electrocardiogram and its patency or otherwise was determined.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean (SEM) and differences between groups were assessed by a Student's unpaired *t* test. Differences between discrete variables were assessed by χ^2 tests with Yates's correction. In all cases a value of $p < 0\cdot05$ was regarded as significant.

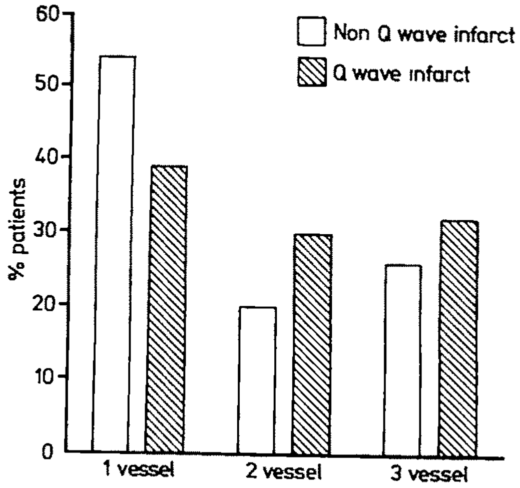

Figure 1 *Distribution of coronary artery disease.*

Results

Of the 339 patients in the study 87 (26%) were classified as having sustained a non Q wave infarction on the basis of their electrocardiographic changes. Table 1 shows the baseline characteristics of these patients and those with Q wave infarctions. The mean ages of the groups were similar but there were more female patients in the non Q wave group (23%) than in the Q wave group (11·5%; $p < 0\cdot02$). In addition, anterior infarction was more common in the non Q wave group (63% *v* 44%; $p < 0\cdot01$).

EXERCISE TESTS

Table 2 summarises the exercise test characteristics of the patients with non Q wave and Q wave infarcts. The mean exercise time was similar in the two groups as was the final double product. Negative tests were as common in the group with Q wave infarction as in the group with non Q wave infarction (49% and 45% respectively) and among those with positive tests silent and painful ischaemia were distributed equally between the two groups.

CORONARY ARTERIOGRAPHY

Coronary arteriography was undertaken in 149 patients, 114 from the Q wave group and 35 from the non Q wave group, representing 45% and 43% of the groups respectively. Figure 1 shows the frequencies of single, double, and triple vessel disease. The trend towards more single (54%) and less double vessel disease (20%) in the non Q wave group compared with the Q wave group (39% and 30% respectively) did not reach statistical significance. Triple vessel disease was equally common in the two groups (26% *v* 32%).

Significantly more patients in the group with non Q wave infarction had a patent infarct related artery (27 (77%)) than those in whom a Q wave infarct occurred (52 (46%)) ($p < 0\cdot01$).

SUBSEQUENT CARDIAC EVENTS

Figure 2 shows the mortality and reinfarction and angina rates at one year for the two groups. Two patients from the group with non Q wave infarction died (2%) and 14 (5%) from the group with Q wave infarction (NS). Reinfarction rates were also similar (8% and 9% respectively) as was the subsequent development of angina pectoris (38% and 43% respectively). In the group with non Q wave infarction seven patients either died or had reinfarctions in the first year and five of them had a positive exercise test (71%) compared with 28 patients in the Q wave group with either complication of whom 23 (82%) had a positive exercise test.

Table 1 *Baseline variables*

Variable	*Non Q wave (n=87)*	*Q wave (n=252)*
Age (years) (mean (SD))	52·3 (0·5)	53·8 (0·3)
Female (No (%))	20 (23)	29 (11·5)*
Anterior site (No (%))	55 (63)	110 (44)**
Inferior site (No (%))	32 (37)	142 (56)**

*p < 0·02, **p < 0·01.

Table 2 *Exercise test characteristics*

Characteristic	*Non Q wave (n=87)*	*Q wave (n=252)*
Exercise time (min)	12·4 (0·6)	11·8 (0·3)
Double product (HR × SBP × 10^{-2})	177 (5·3)	176 (3·3)
Negative test (No (%))	43 (49)	113 (45)
Silent ischaemia (No (%))	22 (25)	60 (24)
Painful ischaemia (No (%))	22 (25)	79 (31)

HR, heart rate; SBP, systolic blood pressure

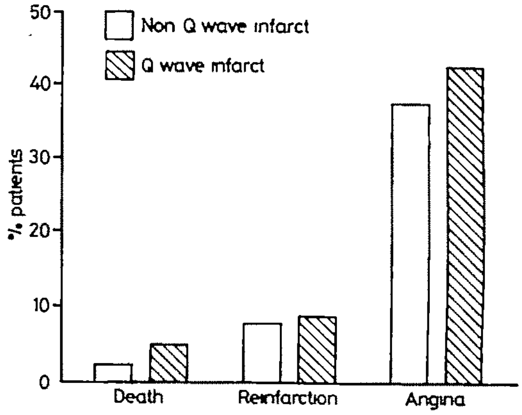

Figure 2 *One year mortality and reinfarction and angina rates.*

CORONARY ARTERY SURGERY

Coronary artery bypass surgery was only undertaken in those patients in whom symptoms could not be controlled by medical treatment. Twelve (14%) patients with non Q wave infarction and 32 (13%) of those with Q wave infarcts had coronary artery surgery.

Discussion

In this study non Q wave infarction was common. It was found in 26% of patients who performed a predischarge exercise test. Others have reported a similar incidence with figures ranging from 16% to 29%.[1 4 9] Thus patients with non Q wave infarction make up a substantial group.

We showed similar exercise test characteristics in Q wave and non Q wave groups, with just under half of the patients in each group having a negative test. It could be argued that a submaximal test might have understressed the group with non Q wave infarction but Sia *et al* using a symptom limited test at 6 days found negative tests in 41% of patients with non Q wave infarcts.[10] In addition, Sia *et al* found a negative test to have been highly predictive of the absence of triple vessel disease or a critical stenosis.

The finding of similar disease severity at angiography in the two groups in this study accords with their exercise test findings and confirms the work of Ogawa *et al* who found frequencies of multivessel disease to be equal in Q wave and non Q wave infarcts (51% and 53% respectively).[11] Similar findings were also reported by Madigan *et al*.[12] The demonstration of a significantly higher patency rate of the infarct related artery in the patients with non Q wave infarcts in this study accords with the current hypothesis that many non Q wave infarcts are the result of either a subtotal occlusion of the relevant artery or caused by spontaneous reperfusion. DeWood and colleagues reported a similar finding in patients with non Q wave infarcts studied one week after admission.[3]

We did not find that the incidence of subsequent cardiac events was higher in those with non Q wave infarcts than in those with Q wave infarcts; unlike Hutter *et al* who reported a significantly increased reinfarction rate nine months after discharge in patients with non Q wave infarcts.[5] In that study, however, the 18 month survival rate was identical in the two groups, suggesting that the overall prognosis was similar—as we report. In addition, there was no increase in the number of patients with angina at two years although Cannom and workers reported an increased frequency of angina in survivors of non Q wave infarction.[13] Ogawa *et al* also reported an increased reinfarction rate in those with non Q wave infarcts.[11] In a study of 593 patients Krone *et al* reported a two year mortality of 3·2% after non Q wave infarction and noted a particularly favourable outcome in those under 60 years.[9] This was again reported in a large recent study by Nicod and colleagues who showed that the prognosis in patients with non Q wave infarcts who were aged less than 70 years was similar to that found in those with Q wave infarctions.[14] Our data seem to confirm these reports, because all our patients were ⩽ 70. Finally, Boden *et al* showed that patients in whom the features of non Q wave infarction do not fit a defined anatomical pattern have an improved short term and long term prognosis,[15] further emphasising the point that non Q wave infarction is not necessarily associated with a high incidence of subsequent cardiac events.

We showed that non Q wave infarction was common; we found it in a quarter of patients undertaking a predischarge exercise test. In such patients the exercise test characteristics and coronary anatomy were similar to those in patients with Q wave infarction. In addition, the one year prognosis and incidence of recurrent infarction and angina were similar in the two groups, suggesting that in patients aged ⩽ 70 years a non Q wave infarction could be managed the same way as a Q wave infarct. After a non Q wave infarction the predischarge exercise test remains a good discriminator of patients at risk of subsequent cardiac events.

None of our patients were treated by thrombolysis, however; and because its frequent use may change the course of non Q wave infarction further studies will be needed in patients with non Q wave infarcts.

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Concentrations of plasma atrial natriuretic factor during and after reversion of ventricular tachycardia

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Abstract

Plasma concentrations of immunoreactive atrial natriuretic factor were considerably increased (mean 745 (376) pg/ml) in 15 patients during spontaneous ventricular tachycardia. There was no significant relation, however, between concentrations of plasma atrial natriuretic factor and systolic arterial blood pressure during tachycardia. Samples taken 30 minutes and 24 hours after reversion of ventricular tachycardia to sinus rhythm showed that, although plasma concentrations of atrial natriuretic factor had fallen significantly, they were still raised after 24 hours. Raised concentrations of atrial natriuretic factor during ventricular tachycardia did not seem to contribute significantly to the hypotension that is often associated with the arrhythmia.

Mammalian atrial tissue has been shown to contain secretory-like storage granules with characteristics similar to those of endocrine peptide secretory cells.[1 2] These granules contain a polypeptide hormone, which is first synthesised as a 151 amino acid prohormone.[3 4] The prohormone is further processed to several smaller peptides, one of which is α natriuretic polypeptide, or atrial natriuretic factor, a 28 amino acid polypeptide with potent natriuretic and diuretic properties.[5 6]

A considerable body of evidence suggests that atrial natriuretic factor may help maintain sodium ion and water balance and modulate the renin-angiotensin-aldosterone system.[7] In addition, a moderate vasodilatory effect has been reported after infusion of atrial natriuretic factor in humans.[8] The major stimulus for release of atrial natriuretic factor into the blood stream is atrial distension, as occurs in congestive cardiac failure, although recent studies suggest that atrial natriuretic factor released from abnormal ventricular myocardium, may also contribute.[9 10]

Plasma concentrations of atrial natriuretic factor are raised in patients with supraventricular tachycardias, but they also seem to rise during ventricular tachycardia; however, fewer patients with this arrhythmia have been studied.[11 12] Because patients with ventricular tachycardia often have severe ventricular dysfunction, atrial natriuretic factor concentrations may be extremely high, owing to combined atrial natriuretic factor release from atrial and ventricular sites. The aim of this study was to examine the pattern of atrial natriuretic factor release during ventricular tachycardia, and evaluate whether this can contribute appreciably to the haemodynamic changes after the onset of tachycardia.

Patients and methods

PATIENTS

This study was carried out within the guidelines set down by the National Health and Medical Research Council of Australia and was approved by the hospital human ethics committee.

We studied 15 male patients (mean age 68·2 (8 9 years)), who had presented with spontaneous sustained ventricular tachycardia that was remote from (> 1 week) acute myocardial infarction. All patients had had at least one documented myocardial infarction, and seven patients had coronary artery disease confirmed by coronary angiography. Ventricular tachycardia was diagnosed by 12 lead electrocardiography recorded at a standard speed (25 mm/s) and amplitude (1 mV/cm). Multichannel simultaneous recordings were obtained in all cases. The electrocardiograms were reviewed by two experienced electrocardiographers and the following diagnostic criteria for ventricular tachycardia were applied in each case: (*a*) sustained wide QRS (>0·12 s) tachycardia (>100 beats/min); (*b*) presence of atrioventricular dissociation; (*c*) typical QRS configuration in V1 and V6 as described by Wellens *et al.*[13]

Ventricular tachycardia was confirmed by transoesophageal electrocardiography in two patients and by electrophysiology study in another seven patients.

Patients were interviewed and the duration of ventricular tachycardia determined. Systolic arterial blood pressure was measured indirectly by a bladder cuff sphygmomanometer and a blood sample was taken after insertion of a peripheral intravenous line and before attempted reversion. Two subsequent samples were taken 30 minutes and 24 hours after reversion to sinus rhythm.

All patients had chronic ischaemic heart disease, and left ventricular function was assessed by radionuclide ventriculography.[14] In addition, M mode echocardiograms were recorded by a Diasonics DRF 400 with a 3·5 or 5 MHz transducer to measure left atrial diameter 24 hours after reversion to sinus rhythm. Patients were studied in the left semilateral position, and recordings were taken

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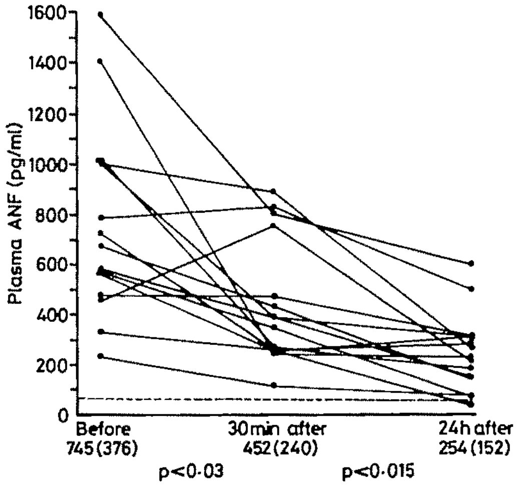
Plasma concentrations (mean SD) of atrial natriuretic factor (ANF) (1 pg/ml = 0·325 pmol/l) before, and 30 minutes and 24 hours after reversion in 15 patients with ventricular tachycardia. The normal range is also shown.



from the parasternal long axis view at the level of the aortic root.[15]

Thirteen patients were receiving concomitant medication when they were studied. This included an antiarrhythmic drug in nine, diuretic in six, calcium channel blocker in three, angiotensin converting enzyme inhibitor in two, and β blocking agent in one patient. Finally, renal function was assessed; plasma creatinine concentrations were within the normal range (0·06–0·12 mmol/l) in all but three patients (0·3, 0·15, and 0·14 mmol/l).

BLOOD COLLECTION AND RADIOIMMUNOASSAY OF ATRIAL NATRIURETIC FACTOR IN PLASMA

Venous blood (10 ml) was obtained via the antecubital vein and collected into a chilled tube containing EDTA and aprotinin (10 000 units; Bayer, Australia). Plasma was separated immediately by centrifugation, snap frozen, and stored at −20°C until assay. Plasma was extracted and atrial natriuretic factor concentration was determined by radioimmunoassay under non-equilibrium conditions at 4°C. The method has been previously described in detail elsewhere.[11]

CONCENTRATIONS OF ATRIAL NATRIURETIC FACTOR IN CONTROLS

Atrial natriuretic factor was measured in blood samples from 34 normotensive healthy volunteers (14 male, 20 female) with normal dietary intake of sodium and normal electrolytes. The upper and lower limits of the normal range were 70 pg/ml and 4 pg/ml and no sex dependent differences were found (men 36 (14) pg/ml, women 33 (16) pg/ml (mean (SD)).

Results

The figure shows plasma concentrations of atrial natriuretic factor before and after reversion to sinus rhythm in the 15 patients with spontaneous ventricular tachycardia. During ventricular tachycardia, all patients had atrial natriuretic factor concentrations well above the upper limit of normal in this laboratory (70 pg/ml). The table shows that ventricular tachycardia was reverted to sinus rhythm by brief overdrive pacing (usually 5–10 seconds ventricular pacing at a rate 10–20 beats/min faster than the ventricular tachycardia rate) in five patients, DC cardioversion after intravenous midazolam sedation in four patients, intravenous amiodarone (350 mg) in three patients, intravenous lignocaine (100 mg) in two patients, and intravenous sotalol (120 mg) in one patient. In 13 patients concentrations of plasma atrial natriuretic factor fell 30 minutes after reversion, but not to within the normal range in any patient. In two patients plasma atrial natriuretic factor concentrations increased; one was treated with intravenous amiodarone and the other by overdrive ventricular pacing. The mean concentration of plasma atrial natriuretic factor was 745 (376) pg/ml before reversion and 452 (240) pg/ml 30 minutes after reversion ($p < 0·03$ by Student's paired t test). The fall in concentration of atrial natriuretic factor was apparently independent of the mode of reversion of ventricular tachycardia. After 24 hours, the mean concentration of plasma atrial natriuretic factor had fallen further to 254 (152) pg/ml ($p < 0·015$) but was still raised, and only one patient was within the normal range. This contrasts with findings in a previous group of 23 patients with supraventricular tachycardia reported from this laboratory.[11] Among this group of patients, plasma atrial natriuretic factor concentrations fell from a mean of 256 (43) pg/ml during supraventricular tachycardia to a mean of 120 (19) pg/ml within 30 minutes of reversion, with levels in five patients falling to within the normal range.

Relation between clinical findings, method(s) of reversion of ventricular tachycardia, and plasma atrial natriuretic factor concentrations

Case No	SHD	Drug	EF (%)	LAD (mm)	VT (beats/min)	Duration (min)	BP (mm Hg)	Reversion	ANF (pg/ml) During	ANF (pg/ml) 30 min	ANF (pg/ml) 24 hours
1	CAD	D/A	31	60	150	120	140	DC	330	263	290
2	CAD-An	D/C	15	45	145	15	135	Am	792	833	500
3	CAD	A	51	50	150	200	90	Pace	475	475	318
4	CAD	—	30	35	190	35	90	Pace	1000	394	150
5	CAD	D/A/Cá	43	29	150	130	140	Pace	567	350	81
6	CAD	β	43	—	160	10	100	Pace	675	439	149
7	CAD-An	A	56	40	200	90	70	DC	723	257	47
8	CAD	A	37	42	120	10	160	Lig	574	375	318
9	CAD-An	A/Cá	37	46	150	60	90	Lig	1000	891	270
10	CAD	—	47	41	160	90	140	Pace	790	270	189
11	CAD	D/A/C	15	—	210	5	120	Am	459	758	223
12	CAD-An	Cá	24	37	180	18	110	Sot	1409	245	236
13	CAD	A	43	45	130	200	100	DC	559	254	350
14	CAD-An	D/A	27	—	200	5	140	Am	236	115	91
15	CAD	D	25	45	170	60	90	DC	1591	810	600

SHD, structural heart disease; EF, ejection fraction; LAD, left atrial dimension, VT, ventricular tachycardia, BP, systolic arterial blood pressure, ANF, atrial natriuretic factor, CAD, coronary artery disease; An, left ventricular aneurysm; DC, direct current cardioversion, Am, amiodarone; Pace, overdrive pacing, Lig, lignocaine, Sot, sotalol; D, diuretic, A, antiarrhythmic drug, C, angiotensin converting enzyme inhibitor, Cá, calcium blocker, β, β blocker

The duration of spontaneous ventricular tachycardia (mean (SD) 69·9 (67) minutes) had no apparent effect on plasma atrial natriuretic factor concentrations; two patients had raised plasma atrial natriuretic factor concentrations (236 and 459 pg/ml) with ventricular tachycardia lasting only five minutes. Similarly, the rate of ventricular tachycardia (mean cycle length 374 (58) ms) did not seem to influence plasma atrial natriuretic factor concentrations.

There seemed to be a weak inverse relation between plasma atrial natriuretic factor concentrations during ventricular tachycardia and systolic arterial blood pressure, but this was not statistically significant ($r = -0·3$; $p = 0·11$ by Spearman's test).

All patients had chronic ischaemic heart disease with a mean left ventricular ejection fraction of 34·9 (12·4)%. In 12 patients the ejection fraction was $<45\%$, but this measurement had no apparent influence on plasma atrial natriuretic factor concentrations during and 30 minutes after reversion of ventricular tachycardia. Furthermore, there was only a weak non-significant inverse relation between the ejection fraction and atrial natriuretic factor concentrations measured at 24 hours after reversion to sinus rhythm ($r = -0·3$; $p = 0·11$).

Finally, mean left atrial dimension measured 24 hours after reversion to sinus rhythm by M mode echocardiography was 43·8 (7·7) mm; it was >40 mm in eight patients.

Discussion

Our results show that patients with spontaneous ventricular tachycardia have considerably higher plasma concentrations of atrial natriuretic factor than healthy controls. These results are consistent with earlier studies of smaller numbers of patients and studies in which ventricular tachycardia was induced during programmed ventricular stimulation or simulated by rapid ventricular pacing.[12 16–19] Given that atrial natriuretic factor has natriuretic and diuretic properties that are potentially beneficial in patients with ventricular tachycardia, the increase may account for the polyuria that is occasionally reported in these patients.[20 21] Although polyuria was not reported by any of our patients, this may be because other neurohormonal reflexes were stimulated by the decreased cardiac output during ventricular tachycardia. These include activation of the sympathetic and renin-angiotensin-aldosterone systems, which would favour oliguria.[16 22] Similarly, the vasodilatory action of atrial natriuretic factor may have been modified by stimulation of catecholamines and vasopressin release during ventricular tachycardia.[16]

Plasma concentrations of atrial natriuretic factor seem to rise as early as five minutes after the onset of ventricular tachycardia and remain raised during prolonged periods of tachycardia, apparently independently of the severity of underlying left ventricular dysfunction or rate of ventricular tachycardia. Because atrial dimension, pressure and rate were not routinely measured during ventricular tachycardia, we cannot comment on the possible influence(s) of these variables on atrial natriuretic factor release. Increases in left atrial dimension however, were reported within minutes after the onset of induced ventricular tachycardia.[16] After reversion of ventricular tachycardia, plasma concentrations of atrial natriuretic factor fell slowly and were still significantly raised 24 hours after reversion to sinus rhythm. This may be explained by impaired renal clearance of atrial natriuretic factor in our patients who generally had poor left ventricular function with reduced cardiac output. In addition, left atrial dimension remained increased in eight patients, and continued atrial natriuretic factor release might also contribute to high post-reversion plasma atrial natriuretic factor concentrations.

Spontaneous ventricular tachycardia is associated with considerably raised concentrations of plasma atrial natriuretic factor which fall slowly and apparently independently of the mode of reversion whether this is pharmacological or non-pharmacological.

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What is meant by a "controlled" ventricular rate in atrial fibrillation?

John M Rawles

Abstract

Reduction of a rapid ventricular rate in atrial fibrillation results in a longer diastolic filling period and a higher left ventricular stroke volume but this is offset by reduced contractility and fewer beats per minute; the net effect on cardiac output is uncertain. Sequences of stroke distances were measured by Doppler ultrasound in 60 resting patients with atrial fibrillation to determine the relation between ventricular rate and linear cardiac output. The slope of the cardiac output/ventricular rate relation was positive in all 20 patients with a ventricular rate < 90 beats per minute and negative in 16 (40%) of 40 patients with a ventricular rate > 90 beats per minute. In atrial fibrillation the ventricular rate can be regarded as "controlled" when the cardiac output/ventricular rate slope is positive and "uncontrolled" when the slope is negative—that is when reduction of ventricular rate would lead to increased cardiac output. As so defined, ventricular rate at rest was controlled in every patient when the ventricular rate was < 90, controlled in 44 (73%) patients when the ventricular rate was 90–140 beats per minute, and uncontrolled in every case when it was > 140 beats per minute.

Achieving a target ventricular rate of 90 beats per minute in patients with atrial fibrillation at rest would result in control with the least compromise of cardiac output.

Reduction of a rapid ventricular rate in atrial fibrillation increases the diastolic filling period and left ventricular stroke volume,[1 2] but this is offset by reduced contractility and fewer beats per minute. The net effect on cardiac output is uncertain. A standard textbook recommends maintaining the ventricular rate at 50–90 beats per minute at rest and 90–115 beats per minute during exercise,[3] with the implicit intention of maximising cardiac output. None the less, the ventricular rate at which cardiac output in atrial fibrillation is maximal is not known nor is the extent of individual variation.

The objectives of this study in patients with atrial fibrillation were to develop a method of predicting the effect of a change of ventricular rate on cardiac output, to determine the ventricular rate for maximal cardiac output, and to find the extent of the variation between individuals. The concept of "control" of the ventricular rate in atrial fibrillation was reexamined in the light of these findings. The intention here is not to apply the method to individual patients but to see what general conclusions can be drawn about the relation between ventricular rate and cardiac output in atrial fibrillation.

In atrial fibrillation there is spontaneous beat to beat variation of ventricular rate around the mean value: analysis of the effect of these changes on stroke output makes it possible to estimate the effect of a change in mean ventricular rate on cardiac output. Once the relation between previous RR intervals and stroke output is obtained it can be transformed to give the relation between ventricular rate and cardiac output.

Most of the beat to beat variation of stroke output can be explained in terms of the two previous RR intervals used in a quadratic polynomial equation.[4] Adjustment of each patient's unique equation enables the ventricular rate at which cardiac output is maximal to be estimated together with the slope of the cardiac output/heart rate relation. Only if the slope is negative will a reduction of ventricular rate lead to an increase of cardiac output.

Patients and methods

I studied 60 patients (24 women and 36 men, mean age 68, mean ventricular rate 103 beats per minute) with chronic atrial fibrillation, who were derived from a consecutive series of 70. In 10 recordings were unreadable in parts. Atrial fibrillation was idiopathic in 26 and in the remainder it was caused by mitral valve disease (13), ischaemic heart disease and/or hypertension (19), thyrotoxicosis (one), and pulmonary embolism (one). Twenty six patients were treated with digoxin, four with amiodarone, and one with a β blocker. Twenty nine patients were not treated with antiarrhythmic agents.

In each patient aortic blood flow was measured by continuous wave ultrasound directed at the arch of the aorta from a transducer held in the suprasternal notch.[5] The Doppler shift frequencies were subjected to spectral analysis and displayed in real time on a paper trace on which a single lead of the electrocardiogram was co-recorded at a paper speed of 50 mm/s. The stroke distance (systolic velocity integral) of each beat was measured by triangulation or planimetry and the sequence of RR intervals and stroke distances was recorded on disc. The mean number of beats studied was 215 (range 100–500). For each patient multiple regression analysis of stroke distance against

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the two previous RR intervals was carried out according to the equation:

$$Sd = a + b(RR\text{-}1) + c(RR\text{-}1 - 750)^2 + d(RR\text{-}2) + e(RR\text{-}2 - 750)^2$$

where Sd is stroke distance, RR-1 the previous RR interval, RR-2 the pre-previous RR interval, and a to e are coefficients. The derivation of this mathematical model has been fully described.[4]

Rearrangement of this equation gives the relation between heart rate and minute distance (minute distance = stroke distance × heart rate), from which the predicted heart rate at which minute distance would be expected to be maximal was obtained, together with the slope of the minute distance/heart rate curve at the point of mean heart rate. The slope was expressed as minute distance (as a percentage of the age predicted normal value)/(beats per minute).

The result of the computer analysis was available within a few minutes of taking the ultrasound recording at the patient's bedside.

Results

MEAN STROKE AND MINUTE DISTANCE

For the whole group of 60 patients with atrial fibrillation mean stroke distance was 64% and mean minute distance 85% of the age adjusted normal values for sinus rhythm[5]—a highly significant reduction in each case ($p < 0.001$). Minute distance was reduced less than stroke distance because ventricular rate was above normal. The mean value of the multiple correlation coefficient, relating stroke distance to RR intervals in each individual, was 0·82 (range 0·68–0·94).

RELATION BETWEEN SLOPE OF MINUTE DISTANCE/HEART RATE CURVE AND VENTRICULAR RATE

Figure 1 shows the relation between the slope of the minute distance/heart rate curve and ventricular rate. For lower heart rates the slope was positive and for higher rates it was negative; the regression line intercepted the line of slope zero, corresponding to maximal cardiac output, at a heart rate of 122 per minute. On average, reduction of heart rate below this rate will reduce minute distance; above this rate minute distance will be increased, but there is wide individual variation. The average slope for the seven patients with ventricular rates of more than 140 per minute is −0·65, indicating an increase of minute distance of 6·5% of the age-predicted normal value for a reduction of ventricular rate of 10 beats per minute.

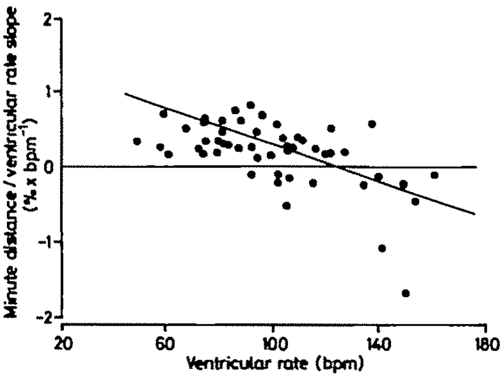

Figure 1 Plot of the slope of the minute distance/ventricular rate curve and mean ventricular rate in patients with atrial fibrillation. The regression line crosses the line of slope zero at a ventricular rate of 122.

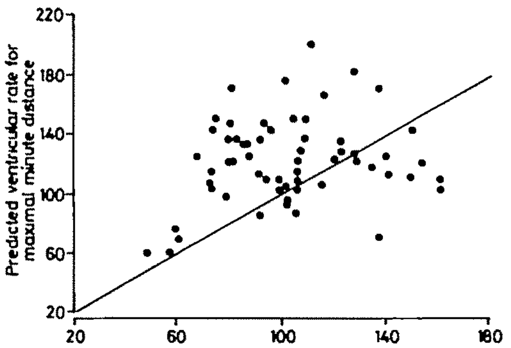

Figure 2 Plot of mean ventricular rate and predicted ventricular rate for maximal minute distance. The line of identity is shown.

PREDICTED VENTRICULAR RATE FOR MAXIMAL MINUTE DISTANCE

The group mean (SD) ventricular rate was 103 (26·6) beats per minute (range 49–161 beats per minute). The mean predicted ventricular rate for maximal minute distance, derived from the multiple regression equations, was 122 (28·8) (range 60–200 beats) per minute. Figure 2 shows a plot of ventricular rate and predicted ventricular rate for maximal minute distance. In 44 (73%) cases the predicted ventricular rate for maximal minute distance was more than the measured ventricular rate (above the line of identity in fig 2) but in 16 (27%) it was lower (below the line of identity in fig 2). All 16 patients with a ventricular rate above that predicted for maximal minute distance had a ventricular rate over 90 beats per minute. In none of the 20 patients with a ventricular rate < 90 did the ventricular rate exceed the predicted ventricular rate for maximal minute distance. In all seven patients with a ventricular rate of $\geqslant 140$ the ventricular rate exceeded that predicted for maximal cardiac output, and the slope of the minute distance/ventricular rate curve was therefore negative.

Figure 3 shows the cumulative total of patients with various ventricular rates and the number of patients whose ventricular rates exceeded that predicted for maximal output—that is those whose minute distance/ventricular rate slopes were positive ("controlled").

EFFECT OF IRREGULARITY ITSELF ON MINUTE DISTANCE

The multiple regression equation was obtained by analysis of the beat to beat changes of stroke distance resulting from a sequence of RR intervals of varying duration. If the value of the mean RR interval for the sequence is substituted in the multiple regression equation then stroke distance, and hence minute distance, is calculated for the circumstances in which all RR intervals have an identical duration. The difference between this value and measured minute distance for the sequence is

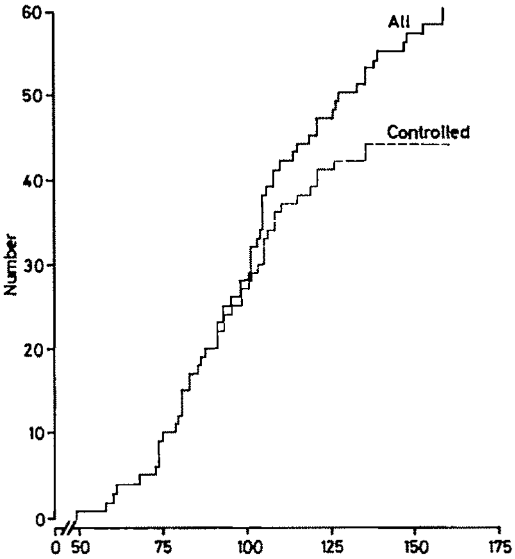

Figure 3 Cumulative totals of all patients and those with "controlled" atrial fibrillation at various ventricular rates.

an indication of the effect of irregularity itself on minute distance. For the whole group, measured minute distance (SD) was 96 (3·2%) of the calculated value, indicating that irregularity of ventricular rate results in an average fall of minute distance of 4%.

There were no distinctive differences in the multiple correlation coefficients, minute distance, or predicted ventricular rate for maximal cardiac output between different aetiological groups or treatments.

Discussion

I measured linear cardiac output non-invasively using Doppler ultrasound. The basic measurement is the systolic velocity integral of aortic blood flow or stroke distance; the product of stroke distance and ventricular rate is minute distance. Stroke and minute distance are linear analogues of stroke volume and volumetric cardiac output respectively.[6]

Beat to beat changes of stroke distance can be described mathematically in terms of the two previous RR intervals in this group of patients with atrial fibrillation.[4] In every patient there was a positive relation between stroke distance and the previous RR interval (RR-1) which was thought to reflect predominantly the diastolic filling of the left ventricle. In all but one patient there was a negative relation with the pre-previous RR interval (RR-2) that was attributed to augmentation of contractility by the force-frequency effect of the shorter RR intervals. Change in the mean duration of RR interval will affect stroke distance not only through diastolic filling of the left ventricle but also by affecting contractility.

Because the mathematical model is based on the physiological principles underlying left ventricular function it can be applied to any case of atrial fibrillation, whatever the ventricular rate, however long the arrhythmia has been present, and however it is caused.

EFFECT OF VENTRICULAR RATE ON CARDIAC OUTPUT

Analysis of the beat to beat changes in stroke distance in patients with atrial fibrillation is used to predict the ventricular rate for maximal cardiac output. This is done by summation of the independent effects of the two previous RR intervals on stroke distance to derive the effect of alteration of the mean RR interval on stroke distance, and hence to predict how mean ventricular rate would influence linear cardiac output. The most reliable section of the minute distance/ventricular rate curve is in the region of the mean ventricular rate where the slope of the curve (that is, whether it is negative or positive) determines the answer to the clinically important question, "If the ventricular rate is reduced will cardiac output rise or fall?"

The slope of the minute distance/ventricular rate curve was always positive for ventricular rates below 90 beats per minute, and as a corollary the predicted ventricular rate for maximum minute distance was always greater than the actual ventricular rate. Conversely, the slope was always negative for ventricular rates above 140 beats per minute, when the predicted ventricular rate for maximum minute distance was lower than the measured ventricular rate. The regression line of slope against ventricular rate passed through zero at a ventricular rate of 122 beats per minute, indicating that on average this was the ventricular rate at which minute distance was maximal (fig 1). The mean predicted value of ventricular rate for maximum cardiac output was also 122 beats per minute. In atrial fibrillation with various causes the average predicted ventricular rate for maximal cardiac output at rest is therefore about 120 beats per minute, with a wide individual variation ranging from 60 to 200 beats per minute. There were no distinctive differences in the shape, position, or fit of the curve relating ventricular rate to linear cardiac output between different aetiological or treatment groups.

All of 16 patients whose ventricular rate exceeded that predicted for maximal cardiac output had a resting ventricular rate greater than 90 beats per minute. Patients with a ventricular rate in excess of that predicted for maximal cardiac output accounted for 40% of those with a ventricular rate over 90, 58% of patients with a ventricular rate over 110, 80% of those with a ventricular rate over 130, and all those with a ventricular rate over 140 beats per minute.

EFFECT OF IRREGULARITY ITSELF ON CARDIAC OUTPUT

If the mean RR interval for each patient is substituted into the multiple regression equation it is possible to calculate the value of minute distance when the mean ventricular rate is identical with that measured, but the rhythm is regular with all RR intervals being of equal duration. The difference between minute distance calculated in this way and measured directly is an indication of the effect on minute distance of irregularity of rate itself. On average, measured minute distance was 4% less than calculated minute distance, suggesting that irregularity of heart rate by itself is not an important cause of reduced cardiac output in atrial fibrillation. The effect of irregularity on cardiac output is determined by the symmetry and shape of the minute distance/heart rate graph and on the frequency distribution of beats with stroke distance above and below average.

COMPARISON OF ATRIAL FIBRILLATION AND SINUS RHYTHM

Atrial fibrillation reduces stroke volume by a loss of atrial contraction, but an increased ventricular rate partially compensates for this and the reduction of cardiac output caused by the arrhythmia is estimated to be 20–30%.[7 8] In the present series, stroke and minute distance were reduced by 36% and 15% respectively, and the mean ventricular rate at 103 beats per minute was 48% higher than the normal values for sinus rhythm predicted by age.[5] The tachycardia of atrial fibrillation is therefore usually a beneficial phenomenon partially counteracting an even greater fall of cardiac output that would otherwise occur, except in those patients in whom the actual ventricular rate exceeds the rate for maximal output.

In our patients with atrial fibrillation, who had a mean ventricular rate of 103, the mean minute distance was 85% of the age-adjusted normal value for patients in sinus rhythm, but if ventricular rate had been reduced to the normal resting value of 70 the estimated minute distance would have been only about 70% of normal.

WHAT IS MEANT BY "CONTROL" OF VENTRICULAR RATE?

When it is applied to the ventricular rate in atrial fibrillation the term "controlled" is generally used loosely to mean "not excessive". Few define precisely what is meant by a controlled rate but Bigger specified 50–90 beats per minute,[3] while Storstein suggested an even narrower range of 60–80 beats per minute[9]; both referred to patients at rest. The mid point of both these ranges is 70, the accepted normal rate in sinus rhythm. However, in sinus rhythm the contribution made to stroke volume by atrial contraction is estimated to be 20–50%, depending on left ventricular compliance and other aspects of left ventricular function.[10 11] In atrial fibrillation, therefore, the ventricular rate needs to be 20–50% higher than in sinus rhythm to maintain a normal cardiac output. The recommendation of a target ventricular rate of 70 in atrial fibrillation seems to disregard completely the haemodynamic consequences of the arrhythmia.

The prediction of the effect of ventricular rate on cardiac output described in this paper is derived from analysis of recordings made from patients with atrial fibrillation at rest. The results should not be extrapolated to exercise, in which—as well as a change of heart rate—there may be alterations of posture, venous return, blood pressure, cardiac contractility, and autonomic tone. The heart rate for maximal cardiac output during exercise therefore differs from that at rest. In sinus rhythm rates of up to 180 beats per minute are achieved during exercise, and it seems likely that rates at least as great as this may be required in atrial fibrillation to maximise cardiac output.

Some workers use the term "control" to mean avoidance of excessive ventricular rates during exercise. Thus David *et al* reported a mean ventricular rate of 139 beats per minute during exercise in patients with therapeutic concentrations of serum digoxin; they wrote that "digitalis alone is ineffective in controlling the heart rate during exercise in many patients with chronic atrial fibrillation".[12] Beasley *et al* compared ventricular rates in patients with atrial fibrillation and serum concentrations of digoxin > 1·6 ng/l with those in controls in sinus rhythm.[13] At rest and at three levels of exercise ventricular rates were 72, 105, 118, 130 in sinus rhythm and 79, 135, 162, and 184 in atrial fibrillation. They considered that in atrial fibrillation the heart rate during exercise was inappropriately high and pointed out that it is not predictable from a knowledge of the resting value. The ventricular rate could therefore be "controlled" at rest but "uncontrolled" during exercise.

Channer *et al* conducted a randomised crossover trial of additional digoxin or verapamil in 14 patients with atrial fibrillation who were already taking digoxin.[14] Although the additional treatment resulted in lower maximal heart rates, the distance walked in 6 minutes was unchanged. Lewis *et al* gave single doses of digoxin, verapamil, and diltiazem, alone and in combination, to six patients with chronic atrial fibrillation.[15] Immediately after exercise lower heart rates were seen with the combination of digoxin and calcium antagonists than with digoxin alone or with placebo. Reduction of the ventricular rate during exercise was associated with a small increase of stroke volume but the benefits of this were offset by a rate related reduction in cardiac output. The highest mean cardiac output was after digoxin alone when the mean ventricular rate was 159 beats per minute. Mean walking distances were not significantly different after any of the treatments.

These data indicate that exercise tolerance is not increased by reduction of ventricular rate. During exercise and at rest a higher ventricular rate is required in atrial fibrillation than in sinus rhythm to maintain cardiac output in the face of the loss of the atrial contribution to stroke output.

A NEW CONCEPT OF CONTROL OF THE VENTRICULAR RATE IN ATRIAL FIBRILLATION

In atrial fibrillation it may be necessary to reduce a rapid ventricular rate for the greater comfort of the patient, or, if mitral stenosis is present, to reduce left atrial pressure and relieve pulmonary oedema. However, in the management of atrial fibrillation the effect that a reduction of rate will have on cardiac output should be considered: ventricular rate should not be reduced arbitrarily irrespective of its effect on cardiac output or exercise tolerance.

I have described a method that for patients at rest provides an answer to the question posed earlier: "If the ventricular rate in atrial fibrillation is reduced will cardiac output rise or fall?" In principle the method could be applied to patients during exercise, but with existing equipment the quality of the recordings would be inadequate for accurate interpretation. Even at rest continuous records of sufficiently good quality could not be obtained in some individuals. The reliability of individual predictions will be the subject of further reports, but from this study on 60 resting patients with atrial fibrillation some general observations can be made.

A "controlled" ventricular rate in atrial fibrillation can be regarded as a rate below that predicted for maximal cardiac output—that is when the slope of the cardiac output/ventricular rate curve is positive and a reduction of rate would lead to a reduction of output. When ventricular rate is "controlled" the circulatory reflexes may adjust the rate according to circulatory needs. Conversely, an "uncontrolled" ventricular rate is above that predicted for maximal cardiac output and reduction of rate would lead to increased output; reflex activity would tend to exacerbate the tachycardia. As so defined, ventricular rate was always controlled at < 90 beats per minute, always uncontrolled at > 140 beats per minute, and uncontrolled in 27% of patients with ventricular rates between 90 and 140.

In atrial fibrillation, a target ventricular rate of 90 beats per minute at rest would be within the range where it can be adjusted by the cardioregulatory reflexes, and cardiac output would be least compromised. During exercise the heart rate that results in maximal cardiac output is likely to be greater than the target rate of 90–115 that has been recommended.[3]

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Range of atrioventricular conduction disturbances in Lyme borreliosis: a report of four cases and review of other published reports

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Abstract

Four patients with Lyme borreliosis had atrioventricular conduction disturbances. All four were positive for specific antibodies against *Borrelia burgdorferi* measured by indirect immunofluorescence tests. Biopsy specimens, which were obtained in three patients, showed bandlike infiltrates of plasma cells and lymphocytes in the endocardium. There was diffuse infiltration of the interstitium of the myocardium by lymphocytes, plasma cells, and macrophages. In two patients single fibre necrosis was seen in the myocardium. Biopsy specimens of the heart showed spirochetes in all three patients and serial sections stained by the Bosma-Steiner technique showed that they resembled *Borrelia burgdorferi*. At follow up one patient had persistent complete atrioventricular block, despite treatment with antibiotics and corticosteroid, and a permanent pacemaker was implanted.

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Lyme borreliosis was first described by Steere *et al* in 1976.[1-3] The disease is caused by the spirochete *Borrelia burgdorferi*[4] which is transmitted by tick or flea bites and it can affect the skin, joints, nervous system, and the heart.[5-8] The disease is found throughout the world but it is especially prevalent in wooded areas of Europe and North America.[6] Lyme borreliosis occurs in three stages with different clinical manifestations.[5-7] In the second stage the heart can be affected, causing atrioventricular block, rhythm disturbances, heart failure, acute myopericarditis, and pancarditis. Cardiac manifestations in Lyme borreliosis were reported in 8% of North American patients.[9] In Europe, however, the frequency of Lyme carditis is not well established yet.

We describe four patients with Lyme borreliosis in whom atrioventricular conduction disturbances caused the main symptoms. They were studied in 1987 and 1988.

Patients and methods

PATIENT 1

A 40 year old athlete was admitted with complete atrioventricular block of unknown origin and a 2 day history of recurrent dizziness and near collapse. For 3 weeks he had had pain and stiffness in four toes of his right foot. He could not recall a tick bite. At physical examination there were no abnormalities, except for a first heart sound of variable intensity and warm, red, and painful toes. The surface electrocardiogram showed a complete atrioventricular block with an escape rhythm of 37 per min and a QRS configuration suggesting a focus in the left bundle branch. The P wave configuration was abnormal and the P wave was long. Despite treatment with atropine and isoprenaline he had recurrent periods of ventricular standstill lasting up to 10 seconds. The erythrocyte sedimentation rate was 22 mm in one hour. Chest radiographs and the echocardiogram were normal. A gallium-67 scan showed diffuse uptake in the myocardium (fig 1a–c). Serological tests for *Borrelia burgdorferi* were positive for IgM and weakly positive for IgG (table). Tests for *Chlamydia* and cytomegalovirus were weakly positive but the titre did not increase. Serological markers for other microorganisms and diseases were all negative, including the *Treponema pallidum* haemagglutination assay, streptococcal antibody tests, tests for several viruses (coxsackievirus, echovirus, adenovirus, influenza A, hepatitis B), rheumatoid factor, and antinuclear antibodies. After giving informed consent, the patient underwent endomyocardial biopsy and serial electrophysiological studies.

PATIENT 2

A 23 year old previously healthy woman was admitted because of a tonic-clonic seizure with collapse, diagnosed as a grand mal epileptic seizure. She could not recall a tick bite. Physical examination showed no abnormalities except a first heart sound of variable intensity. The electroencephalogram and computed tomogram of the brain were normal. A surface electrocardiogram showed complete atrioventricular block with a ventricular escape rhythm of 40 per minute and giant T wave inversion (figure 2). Routine laboratory tests, chest radiographs, and the echocardiogram were normal. Serological tests were positive for *Borrelia burgdorferi* (table) and negative for other micro-organisms. After informed consent was obtained, we performed an electrophysiological study and took endomyocardial biopsy specimens.

PATIENT 3

This 30 year old man had removed ticks from

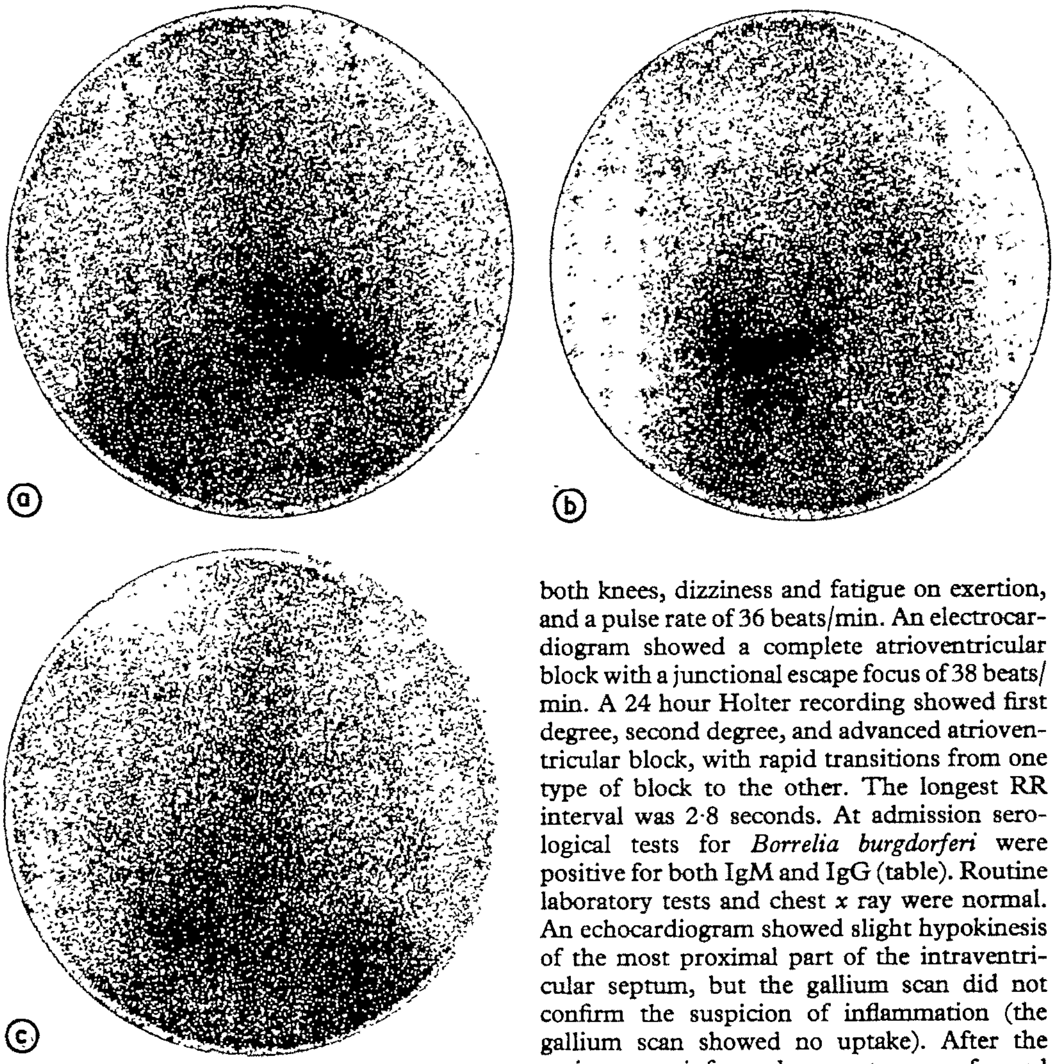

Figure 1 Scan of patient 1 48 hours after intravenous injection of 100 MBq gallium-67. (a) anterior, (b) left lateral, and (c) posterior views showing increased uptake in the cardiac wall.

his cat but did not recall a tick bite. In the next three weeks he felt ill, had abdominal pain, and discovered a red spot (10 cm wide) on the right side of his face, which resembled erythema migrans and disappeared spontaneously after 6 days. Since then he had slight fever, pain in both knees, dizziness and fatigue on exertion, and a pulse rate of 36 beats/min. An electrocardiogram showed a complete atrioventricular block with a junctional escape focus of 38 beats/min. A 24 hour Holter recording showed first degree, second degree, and advanced atrioventricular block, with rapid transitions from one type of block to the other. The longest RR interval was 2·8 seconds. At admission serological tests for *Borrelia burgdorferi* were positive for both IgM and IgG (table). Routine laboratory tests and chest *x* ray were normal. An echocardiogram showed slight hypokinesis of the most proximal part of the intraventricular septum, but the gallium scan did not confirm the suspicion of inflammation (the gallium scan showed no uptake). After the patient gave informed consent, we performed an electrophysiological study and took endomyocardial biopsy specimens.

PATIENT 4

A 34 year old previously healthy male nurse had arthritis of one toe of his right foot for three weeks. Thereafter he noticed palpitation, with-

Data on the four patients with Lyme borreliosis

Patient	IFA		Recalled tick-bite	E(C)M	Arthritis	Neurological illness	AV block			Rhythm disturbance	HF/P	Echocardiogram	Chest x ray	Electrophysiological conduction disturbance			Endomyocardial biopsy specimen		Treatment	Course
	IgM	IgG					1°	2°	3°					I-A	AH	HV	Inflammation	Spirochetes		
1	1:128(+)	1:64(±)	−	−	+	−	+	+	+	−	−	N	N	+	+	+	+	+	Tetracycline, penicillin, temporary pacemaker	Complete resolution
2	1:16(−)	1.128(+)	−	−	−	−	−	−	+	−	−	N	N	−	−	+	±	+	Penicillin, ceftriaxone, corticosteroids, pacemaker implantation	Persisting complete AV block
3	1:512(+)	1:128(+)	−	+	−	−	+	+	+	−	−	A	N	−	+	−	+	+	Penicillin	Complete resolution
4	1.256(+)	1·256(+)	−	−	+	−	+	+	+	−	−	N	N						Penicillin	Spontaneous complete resolution

IFA, immunofluorescence assay; E(C)M = erythema (chronicum) migrans; AV block, atrioventricular block; HF/P, heart failure/pericarditis; I-A, intra-atrial; +, positive/present; ±, weakly positive; −negative/absent; A, abnormal, N, normal.
Antibody titres of *Borrelia burgdorferi* determined with indirect immunofluorescence assay; positive titre for IgM antibodies ≥1:64 and for IgG antibodies ≥1:128 (Laboratory for Public Health, Department of Pathology and Microbiology, Leeuwarden, The Netherlands).

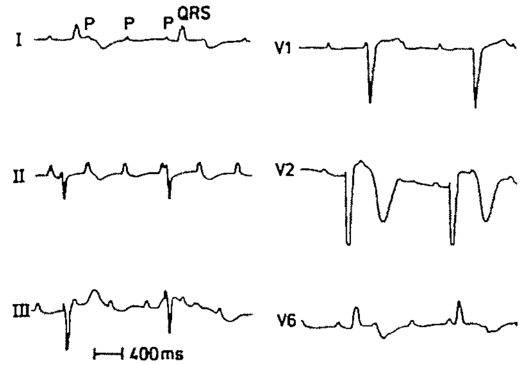

Figure 2 Electrocardiogram of patient 2 on admission showing complete atrioventricular block and giant negative T waves in leads V2 and I, II, V6 (QT_c 474 ms).

out dizziness or other complaints. The surface electrocardiogram showed atrioventricular Wenckebach block. Holter monitoring showed short periods of complete atrioventricular block, Wenckebach block, and first degree atrioventricular block (PQ interval 360 ms) with rapid transition from one type to another. The patient was admitted for further investigation. Physical examination showed only slight signs of arthritis of the right toe. Routine laboratory tests, the chest *x* ray, and echocardiogram were normal. At admission the surface electrocardiogram had reverted to normal and further monitoring did not show any rhythm abnormalities. Therefore an electrophysiological study was not performed nor were biopsy specimens taken. Serological tests showed clear evidence of *Borrelia burgdorferi* antibodies (table) and all other serological tests were normal.

ELECTROPHYSIOLOGICAL STUDIES

We studied patients in the postabsorptive state with 4F bipolar (Cordis) catheter electrodes designed to record His bundle potentials. After positioning of the catheter across the tricuspid valve under fluoroscopic guidance we mapped the His bundle region to characterise the conduction of the atrioventricular node and His bundle and determine the site of the block. In addition, we placed two quadripolar (USCI) catheter electrodes, one in the high right atrium and one in the right ventricular apex. Signals were directly recorded with a Gould ES 1000 recorder, paper speed at 100 mm/s. Programmed electrical stimulation in the right ventricular apex was performed with only one extrastimulus. Overdrive suppression of the escape focus was always interrupted by back up pacing after 3 seconds.

Endomyocardial biopsy specimens were taken at the same session through the right jugular vein with a 7F Cordis bioptome. The specimens were fixed in formalin and embedded in paraffin. Serial sections were cut and every fifth section was stained by a routine technique. All other slices were stained with a modified silver stain to screen the sections for micro-organisms.[10]

Results

We performed electrocardiographic follow up studies on all patients and electrophysiological and endomyocardial biopsies in three of the four patients.

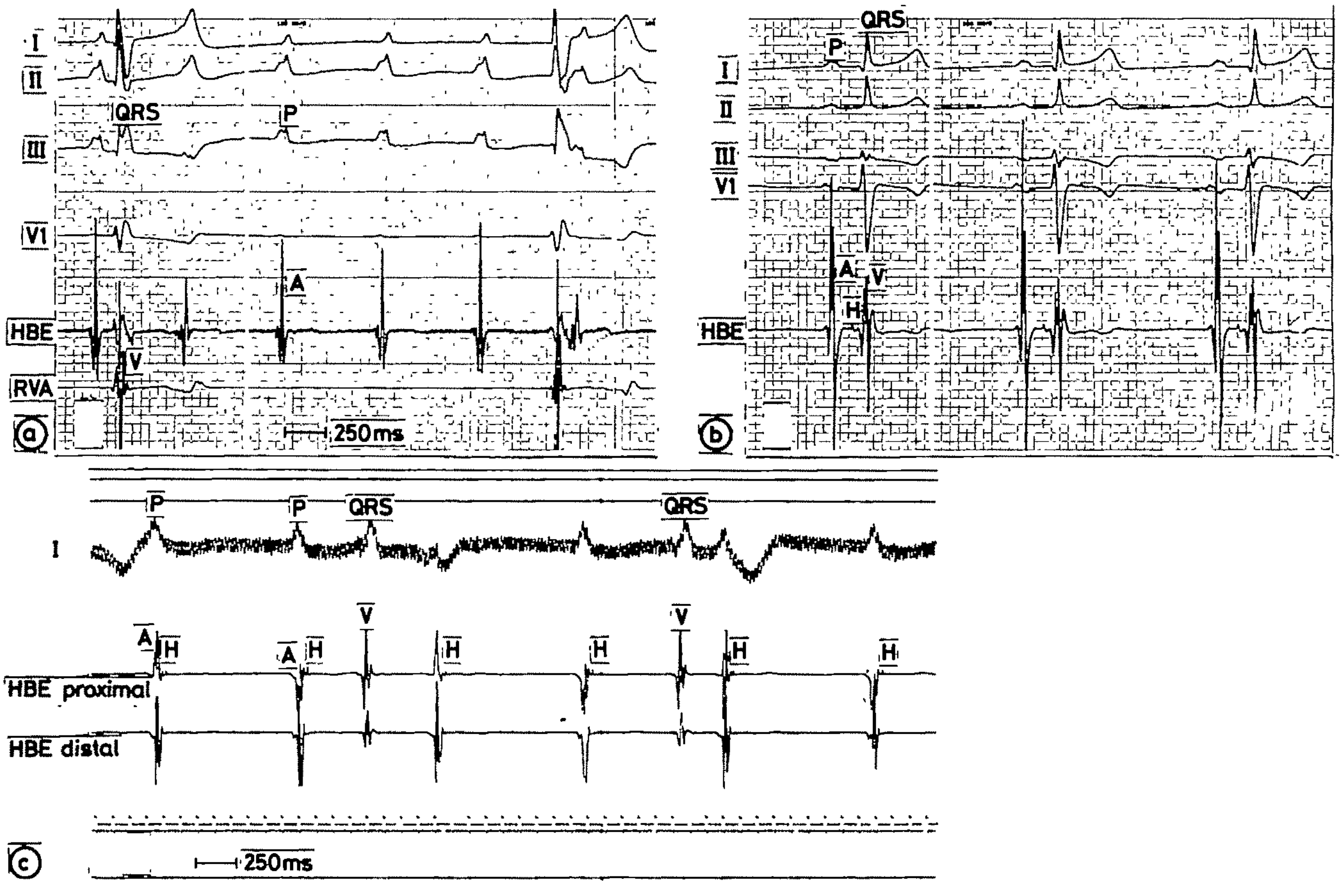

Figure 3 Electrophysiological recordings showing (a) complete atrioventricular block in patient 1 with no His bundle activity (P wave duration 120 ms, QRS duration 130 ms), (b) first degree atrioventricular block (PR interval 280 ms) and a small positive-negative His bundle spike in patient 1 (AH interval 155 ms, HV interval 45 ms, P wave duration 100 ms, QRS duration 100 ms) Electrophysiological recordings (c) in patient 2 showing complete atrioventricular block and (only positive) His bundle activity (AH interval 85 ms). A, atrial activity; H, His spike; HBE, His bundle electrocardiogram; RVA, right ventricular apex; V, ventricular activity.

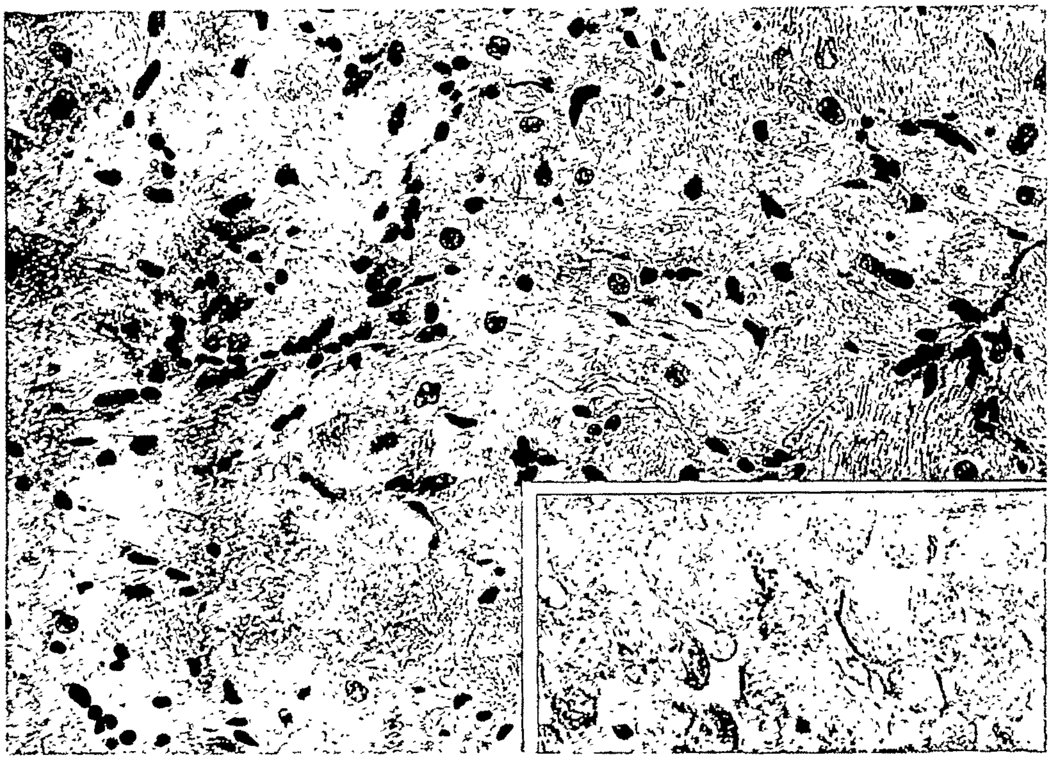

Figure 4 Endomyocardial biopsy specimen from patient 1. (a) Showing diffuse interstitial infiltrates of lymphocytes, plasma cells, and some macrophages in the myocardium (original magnification, × 250, haematoxylin and eosin). (b) A black-stained spirochete between the muscle fibres (original magnification, × 1250, Bosma-Steiner staining)

PATIENT 1

Patient 1 underwent serial electrophysiological investigations. The first electrophysiological study, performed in the acute phase with complete atrioventricular block, showed no His bundle activity despite extensive mapping of the His bundle region with several types of catheter electrodes. The QRS configuration and duration (130 ms) were compatible with an (unstable) escape focus in the left bundle branch. Additionally, the abnormal P wave configuration and duration of 120 ms suggested a prolonged intra-atrial conduction time (figure 3a). There was no retrograde ventriculoatrial conduction, either spontaneous or during ventricular pacing. No ventricular or supraventricular tachycardias were induced.

The finding of a diffuse lymphoplasmacytic infiltrate and scattered macrophages in the myocardium accorded with the gallium-67 scan. A few small infiltrates were found around single myocytes that showed early stages of necrosis. In the oedematous endocardial region plasma cells and lymphocytes formed infiltrates of varying thickness. Vascular alterations were not demonstrable. A few spirochetes were seen between the muscle fibres (figure 4).[11] In combination with the serological results this indicated Lyme carditis.

A temporary pacemaker was inserted and the patient was treated with oral tetracycline (500 mg four times a day); after 5 days this was changed to intravenous penicillin (4 million IU four times a day for 14 days). Between the 6th and 10th days after admission the disturbances of atrioventricular conduction resolved to a second and later to a first degree atrioventricular block on the surface electrocardiogram. The electrophysiological study was repeated in the recovery phase. His bundle activity was now easily found, the intra-atrial conduction delay had disappeared, and the duration of the QRS complex was normal. The AH interval was slightly prolonged, but the HV interval was normal (figure 3b).

After three weeks of antibiotic treatment the patient was discharged with a normal surface electrocardiogram and minor residual complaints of arthritis.

PATIENT 2

Electrophysiological study showed a small positive His bundle deflection without a negative deflection at all sites mapped in the His bundle region. The AH interval was normal, but there was no relation between His bundle activity and QRS complexes (figure 3c). There was no retrograde ventriculoatrial conduction. No ventricular or supraventricular tachycardias were induced. The myocardial biopsy specimens showed small diffuse focal infiltrates of plasma cells and lymphocytes mixed with some macrophages as is seen in other affected organs in the second stage of Lyme borreliosis. Typical band-like infiltrates of plasma cells and lymphocytes were seen in the endocardium. Single muscle fibre degeneration was found in association with small infiltrates of mononuclear cells. Spirochetes were demonstrable in the interstitium by the Bosma-Steiner silver stain.[10 11] The patient was treated with intramuscular penicillin (5 million IU three times a day) for 14 days. Six weeks later a 48 hour Holter scan showed persistent complete atrioventricular block with a ventricular escape rhythm of 32 beats/min. At a bicycle exercise test there was too small an increase in the patient's ventricular escape rhythm for her to attain a normal performance for her age.

Repeated serological tests for *Borrelia burgdorferi* were positive for IgG. Subsequently she was treated with intravenous ceftriaxone (2 g a day for 10 days) and oral prednisolone

(40 mg/day in two doses, tapering by 10 mg/week). After another seven weeks the surface electrocardiogram showed persistence of the complete atrioventricular block and a rate responsive pacemaker was inserted.

PATIENT 3

Electrophysiological study showed a first degree atrioventricular block with an AH interval of 340 ms and a HV interval of 45 ms at a heart rate of 92 min. There was a large biphasic His spike. The PQ interval was 400 ms and the QRS interval 110 ms. There was a prolonged Wenckebach cycle length of 570 ms. No retrograde ventriculoatrial conduction was found. No ventricular or supraventricular tachycardias were induced.

The endomyocardial biopsy specimens showed subendocardial and diffuse interstitial myocardial infiltrates of plasma cells and their precursors. In this patient necrosis of myocytes was not detectable. Few spirochetes were found in the interstitium between the muscular fibres.

The patient was treated with intravenous penicillin (5 million IU four times a day) for 10 days. At first he showed first degree atrioventricular block with rapid transition to complete atrioventricular block, but after 8 days of antibiotic treatment only first degree atrioventricular block was seen (PQ interval decreased to 280 ms). After 10 days the patient was discharged without any complaints. One week after the end of antibiotic treatment the surface electrocardiogram was completely normal.

PATIENT 4

This patient was treated with intravenous penicillin (4 million IU four times a day) for 10 days. Eighteen months later he was well and the conduction disturbances did not recur.

Discussion

The clinical expression of Lyme borreliosis is highly variable.[5-8] The most common and clinically most troublesome cardiac manifestation is atrioventricular block.[5 6 12-15] Among patients with atrioventricular conduction disturbances caused by Lyme borreliosis 98% show first degree atrioventricular block, 40% Wenckebach periodicity, 50% complete atrioventricular block, and about 38% require a temporary pacemaker. Up to 65% of these patients show ST segment depression or T wave inversion, depressed left ventricular ejection fraction, or cardiomegaly and pericarditis.[6] Supraventricular arrhythmias such as atrial fibrillation occur occasionally[16] and one patient can have atrioventricular block of several degrees. Occasionally the degree of atrioventricular block varies within minutes.[6 12 15] According to some the risk of complete atrioventricular block is much higher when the PR interval is >300 ms.[9 17]

The differential diagnosis of the causes of atrioventricular block includes other infections such as *Treponema pallidum* infection, diphtheria, *Yersinia enterocolitica* infection, virus infection (coxsackie A and B, echovirus type 6 and 8, adenovirus type 3, influenza A, hepatitis B, Epstein-Barr, mumps, poliomyelitis, varicella), toxoplasmosis, Chagas's disease, and rickettsial infections. Non-infectious causes of atrioventricular block are coronary artery disease, intracardiac operation, medication induced atrioventricular block, congenital heart disease, idiopathic sclerodegenerative disease (Lenègre's disease), fibrocalcareous enchroachment (Lev's disease), acute rheumatic fever, polyarthritis, systemic lupus erythematosus, amyloidosis, sarcoidosis, and myxoedema. These diseases are usually distinguishable from Lyme borreliosis by special laboratory tests and clinical findings. The tests for Lyme borreliosis measure IgM and IgG antibodies against *Borrelia burgdorferi*.[6-8 18 19] Two types of tests are used: indirect immunofluorescence antibody tests and an enzyme-linked immunosorbent assay (ELISA). The ELISA is more sensitive and specific than indirect immunofluorescence tests, which are more commonly available.[18] Routine laboratory tests usually show a moderately increased erythrocyte sedimentation rate, slight leucocytosis, and raised total immunoglobulin. Chest *x* rays and echocardiograms are usually normal.

Gallium scintigraphy can show increased uptake in the cardiac wall, which suggests endomycarditis.[20-22] Histological detection of *Borrelia burgdorferi* organisms in tissue, blood, cerebrospinal fluid, and joint fluid is feasible,[10 11 23 24] but seldom successful.

In adults early Lyme borreliosis (stage 1) is treated with oral tetracycline (250 mg four times a day) for 30 days and in stages 2 and 3 by intravenous ceftriaxone (2–4 g daily in one or two doses) or intravenous penicillin (20 million IU daily in 4–6 doses) for 10 days.[6 8 25-28] If atrioventricular block persists beyond a week treatment with corticosteroids is advised (40–60 mg/day, tapering by 5–10 mg/week).[7 9 15 25 29-31] The value of a single corticosteroid dose at the start of antibiotic treatment in reducing the risk of a Jarisch-Herxheimer reaction (temporary deterioration of the disease because of an overload of the immunosystem by toxic antigen) is uncertain.

Serological tests for Lyme borreliosis were positive in all four of our patients: patient 1 was positive for IgM antibodies, patient 2 for IgG antibodies, and patients 3 and 4 were positive for both (table). In patient 1 the gallium scan showed signs of endomyocarditis. In all the patients the atrioventricular conduction disturbances caused the main symptoms. In three patients (1, 2, and 4) the clinical presentation did not resemble the classic course of Lyme borreliosis in North American patients: our patients did not have erythema migrans and arthritis was restricted to the small joints and developed before the cardiac symptoms. Only patient 3 had erythema migrans and general malaise before the atrioventricular conduction disturbances developed (table). The clinical expression of Lyme borreliosis is known to vary considerably. In about 25% of the cases with Lyme arthritis there is no erythema migrans or it is not recognised. Sometimes patients present with neurological or cardiac symptoms.[5-8 14 32] Furthermore, the strain of *Borrelia burgdorferi* and the ticks are different in Europe (generally *Ixodes ricinus*) and in the United States (generally *Ixodes dammini* and *Ixodes pacificus*).[33-42]

The atrioventricular conduction disturbances were studied by serial surface electrocardiograms in all four patients and in three serial electrophysiological studies were also performed (figure 3a–c). In three patients we also took endomycardial biopsy specimens. The electrophysiological studies in patient 1 indicated that the atrioventricular block was located in the atrioventricular node, with accompanying conduction disturbances above (intra-atrial) and beneath (in the common His bundle) this site. This patient had a very unstable escape focus. The electrophysiological study in patient 3 also suggested a proximal site for the atrioventricular block, which was more local than in patient 1. Giant T wave inversion, as shown on the electrocardiogram of patient 2 (figure 2), was described in other patients with Lyme borreliosis with more diffuse cardiac involvement[6 9] but inverted T waves were also described in patients who had had a period of circulatory arrest and cerebral hypoxaemia.[43] The electrophysiological study in patient 2 showed no terminal negative deflection of the His spike, a normal AH interval, and no relation between His bundle activity and ventricular complexes (figure 3c). This shows that the site of the atrioventricular block may also lie in the distal part of the His bundle, leaving the proximal part undisturbed. Despite extensive treatment with antibiotics and corticosteroid[9 15 28-30] complete atrioventricular block persisted in this patient and a permanent pacemaker had to be implanted. We believe this to be the first reported case in which complete atrioventricular block caused by Lyme disease did not resolve.[6 12-15 17 44 45]

The biopsy specimens of the hearts of all three patients had the same appearance. The endocardial zone showed the plaque-like infiltrates of lymphocytes and plasma cells that are typical of cardiac involvement in Lyme borreliosis.[46] There were interstitial infiltrates in the myocardium and sometimes signs of necrosis of single myocytes. The tissue of all three patients contained coiled structures typical of the Lyme spirochete. So far only Reznick *et al* have reported a "coiled structure, compatible with a spirochetal organism" in the endomyocardial biopsy specimen of a surviving patient.[31] Marcus *et al* showed spirochetes in the myocardium at a necropsy in a patient with fatal pancarditis related to coexistent Lyme borreliosis and babesiosis.[47]

Both patients 3 and 4 showed spontaneous alteration in the degree of atrioventricular block. Patient 4 had a mild disturbance of atrioventricular conduction—that is short periods of complete atrioventricular block. He was treated with antibiotics and the atrioventricular conduction disturbances did not recur.

These four patients and a review of other reported cases lead to the following conclusions. In Lyme disease electrophysiological studies show that atrioventricular block can occur at different levels of the atrioventricular conduction system. Occasionally there are sinoatrial and intra-atrial conduction disturbances. Ventricular and supraventricular tachycardias seem to be less frequent than conduction disturbances. Spirochetes can be found by a special silver staining technique on the endomyocardial biopsy specimens of patients with Lyme carditis. Usually gallium-67 scintigraphy and endomyocardial biopsies are not essential to the diagnosis of Lyme carditis. Where diagnosis is difficult, however, the combination of serological tests—that are positive for *Borrelia burgdorferi*—and the presence of spirochetes in endomyocardial biopsy specimens (proof of Lyme carditis) may influence the management of a patient, as shown by the extensive antibiotic treatment and late pacemaker implantation in patient 2. It may be worth while to use the gallium scan to guide biopsy and increase the sensitivity of histological examination.[48] When atrioventricular block of unknown origin develops suddenly, Lyme carditis must be considered, especially in younger patients. In most patients adequate treatment will avoid the need for a permanent pacemaker.

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Familial ventricular tachycardia: a report of four families

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Abstract

Four cases of familial ventricular tachycardia are presented. In each family the proband was an adolescent girl. Twelve members in the four families were affected and all were female. The clinical and electrocardiographic features were relatively constant within each family but there were striking differences between families. These differences argue against a common electrophysiological or pathophysiological basis for the ventricular tachycardia.

Familial ventricular tachycardia is rare. Most reported cases have the long QT syndrome or are associated with familial cardiomyopathies. We report four families in which ventricular tachycardia occurred in at least two members. There were important differences between families but the clinical and electrocardiographic features were strikingly consistent within each family.

Case reports

FAMILY A

The proband (fig 1), an apparently healthy 14 year old girl, was found to have an irregular pulse at a routine medical examination. Physical examination, including hearing, was otherwise normal. The resting electrocardiogram showed sinus bradycardia, a PR interval of 120 ms, a QT interval of 420 ms (QTc 438 ms), and very prominent U waves, particularly in right precordial leads (fig 2d). During the recording there were several salvos of non-sustained multiform ventricular tachycardia. She was then symptom free but within 12 months she had several episodes of dizziness and presyncope, after which a 24 hour electrocardiographic recording showed frequent ventricular extrasystoles (> 1800 per hour) and up to 80 episodes of multiform ventricular tachycardia per hour (at rates up to 160 per minute) (fig 3), with almost complete suppression of arrhythmia overnight. She was symptom free during this recording. The arrhythmia was unaltered during an exercise stress test. A Valsalva manoeuvre produced a flat heart rate response with no electrocardiographic changes and no ventricular arrhythmia.

The patient's mother who for several years had been taking phenytoin for "epilepsy" was also investigated. Her syncope always occurred during activity but not necessarily on exertion. Her electrocardiogram was remarkably similar to that of her daughter (fig 2c) and 24 hour electrocardiographic recording showed up to 1800 ventricular extrasystoles per hour and up to 155 episodes of ventricular tachycardia per hour (rate up to 190 per minute) (fig 4) with almost complete suppression overnight.

The proband's father's electrocardiogram was normal. That of her younger sister also showed prominent U waves (fig 2e) but 24 hour electrocardiographic recording showed no arrhythmia. Electrocardiograms from the patient's maternal grandmother (fig 2b) and great-grandmother (fig 2a) also show abnormal U waves. Other family members have normal electrocardiograms (fig 1).

Despite treatment with β blockers, her syncope recurred and a high left cervical sympathectomy was performed. Postoperatively she continued treatment with a β blocker but had further syncope. Prolonged electrocardiographic monitoring showed persisting complex ventricular ectopic activity and no ventricular tachycardia, but there was profound sinus and nodal bradycardia. The β blocker was stopped, and since then she has been symptom free, with no recurrence of tachycardia or bradycardia.

The mother is symptom free on treatment with a β blocker although ventricular arrhythmias are still present on ambulatory electrocardiographic recordings.

FAMILY B

The proband, a 13 year old symptom free girl, was found to have an irregular pulse during a viral illness. Physical examination was otherwise normal. A resting electrocardiogram showed ventricular bigeminy with T wave inversion in inferolateral leads. Ambulatory monitoring showed frequent ventricular extrasystoles (> 2250 per hour), with prolonged periods of bigeminy. Only rarely were there two consecutive sinus beats, but when this did occur a large abnormal U wave was present. Ventricular tachycardia was frequent (1-24 episodes an hour) and was bidirectional (fig 5) or multiform. The tachycardia rate was 170 beats per minute. During a Valsalva manoeuvre the ventricular arrhythmias were abolished but the recording quality precluded measurement of the QT interval. On exercise stress testing the number of ventricular extrasystoles initially increased and then fell, with abolition by stage 5 of the Bruce protocol. The extrasystoles returned during recovery. A cross sectional echocardiogram was normal.

Within nine months severe episodes of dizziness developed but she was not syncopal. On

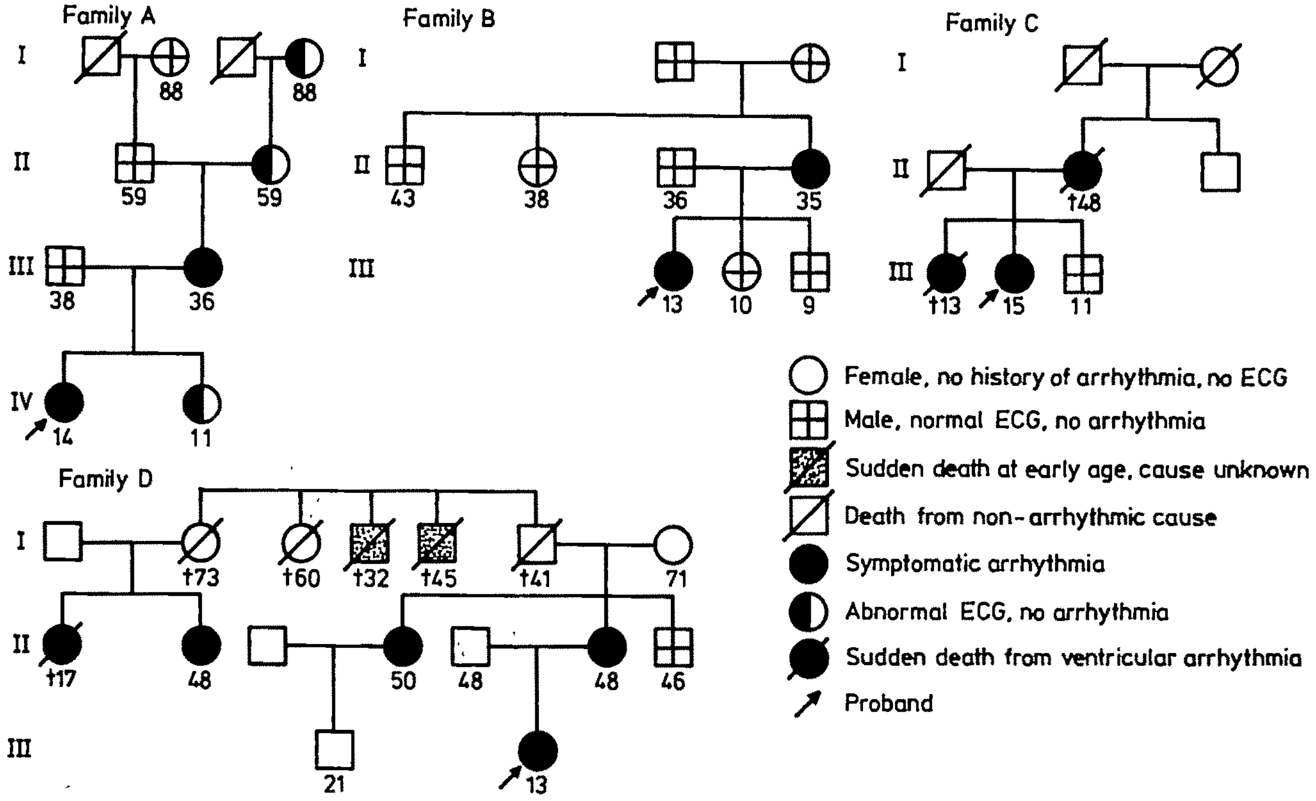
Family A
I
88
88
II
59
59
III
38
36
IV
14
11
Family B
I
II
43
38
36
35
III
13
10
9
Family C
I
II
†48
III
†13
15
11
Family D
I
†73
†60
†32
†45
†41
71
II
†17
48
50
48
48
46
III
21
13
Female, no history of arrhythmia, no ECG
Male, normal ECG, no arrhythmia
Sudden death at early age, cause unknown
Death from non-arrhythmic cause
Symptomatic arrhythmia
Abnormal ECG, no arrhythmia
Sudden death from ventricular arrhythmia
Proband

Figure 1 Pedigrees of the four families

propranolol both her symptoms and the ventricular tachycardia persisted. Mexiletine and atenolol were not tolerated. On flecainide she continued to have almost incessant ventricular bigeminy and short runs of ventricular tachycardia and her symptoms were controlled for a few months but then returned. At an electrophysiology study rapid, non-sustained, multiform ventricular tachycardia could be induced by premature stimuli but induction was not reproducible and could not be used for drug testing. Monophasic action potential recordings showed no evidence of dispersion of ventricular repolarisation. Subsequent treatment with disopyramide produced no improvement in either her symptoms or the arrhythmia. Currently her symptoms are well controlled by amiodarone although monitoring shows that the arrhythmia persists.

The patient's mother volunteered that she had also had an irregular pulse for many years, with no history of syncope or dizziness. Her physical examination was normal. Her electrocardiogram showed frequent ventricular arrhythmias and 24 hour recording showed frequent ventricular extrasystoles (> 2800 per hour) and many episodes (> 18 an hour) of non-sustained bidirectional or multiform ventricular tachycardia (fig 6). Her arrhythmias were also suppressed during the Valsalva manoeuvre and on peak exercise. Electrocardiograms from the patient's brother, sister, and father, and her mother's brother, sister, and parents were normal (fig 1).

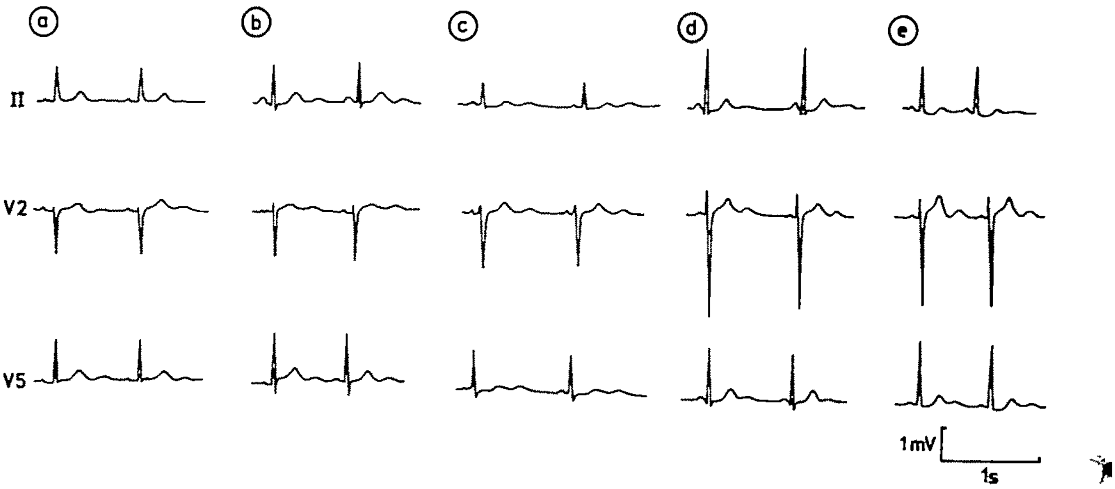

Figure 2 Electrocardiograms (leads II, V2, V5) from members of family A showing prominent U waves. a, maternal great-grandmother (I.4); b, maternal grandmother (II.2); c, mother (III.2); d, proband (IV.1); e, younger sister (IV.2).

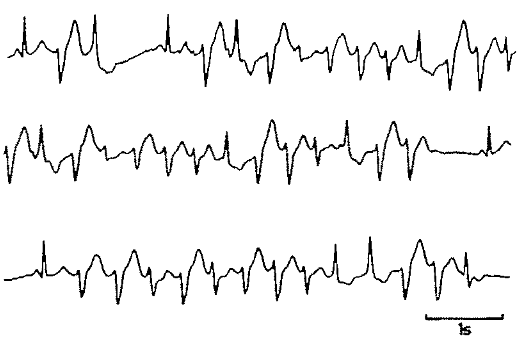

Figure 3 Multiform ventricular tachycardia recorded during ambulatory electrocardiographic monitoring in the proband from family A.

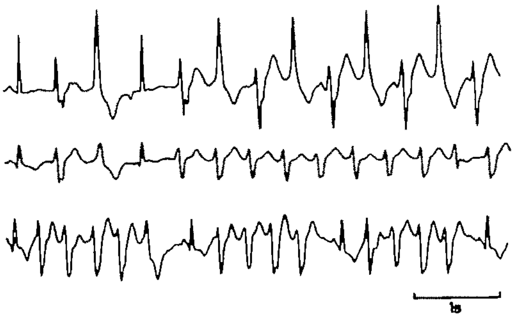

Figure 5 Ventricular tachycardia recorded during ambulatory electrocardiographic monitoring of the proband from family B Several types of ventricular tachycardia were seen including bidirectional tachycardia (upper trace), regular monomorphic tachycardia (middle trace), and irregular multiform ventricular tachycardia (lower trace)

FAMILY C

The proband, a 15 year old girl, was referred after three episodes of presyncope on exercise. Physical examination was normal. The resting electrocardiogram showed ventricular bigeminy and non-sustained ventricular tachycardia. The QT interval could not be measured because consecutive sinus beats were not recorded. Ambulatory electrocardiographic recording confirmed frequent multiform ventricular tachycardia at 160 beats per minute (fig 7). Echocardiography showed a slightly dilated left ventricle. The ejection fraction by radionuclide angiocardiography was normal. Treatment with amiodarone provoked thyrotoxicosis and did not relieve her symptoms. While being treated with flecainide, and with a right atrial AAI pacemaker, she has been symptom free for two years.

In 1966 the patient's mother had heart failure, atrial flutter, and multiform ventricular tachycardia a few months after the birth of her second child (the proband). Cardiac catheterisation and angiography led to a diagnosis of "congestive cardiomyopathy". Although the arrhythmias persisted, the heart failure resolved and there were no symptoms for the next 14 years. In 1980, after a syncopal attack, the electrocardiogram showed frequent ventricular arrhythmias including non-sustained ventricular tachycardia. There was no clinical evidence of heart failure and the left ventricle was only slightly dilated on M mode echocardiography. The mother died suddenly one year later, presumptively from a ventricular arrhythmia.

At necropsy the left ventricle was mildly dilated but there was no important macroscopic or histological abnormality.

The patient's older sister had also presented to another hospital with ventricular arrhythmias and cardiac enlargement and died suddenly at the age of 13 years.

FAMILY D

The proband developed palpitation at the age of 10 years. Investigations at that time were normal; no arrhythmia was seen. She presented again three years later with palpitation, chest pain, and dyspnoea on exertion. She had an irregular tachycardia with no clinical sign of heart failure. The cardiothoracic ratio on chest *x* ray had increased from 100/205 cm to 150/235 cm. The electrocardiogram showed an incessant arrhythmia in which most QRS complexes had a right bundle brunch block pattern (fig 8). Twenty four hour electrocardiographic recording showed frequent sustained arrhythmias of 260 beats per minute. There were never two consecutive sinus beats. The echocardiogram showed a dilated left ventricle with impaired contraction.

An invasive electrophysiological study confirmed fascicular ventricular tachycardia, each ventricular beat being preceded by a fascicular deflection but not by a His potential. Intravenous flecainide acetate abolished the arrhythmia and restored sinus rhythm. Oral flecainide maintained sinus rhythm with occasional ventricular bigeminy. Six weeks after the start of treatment the heart size returned to normal and echocardiography

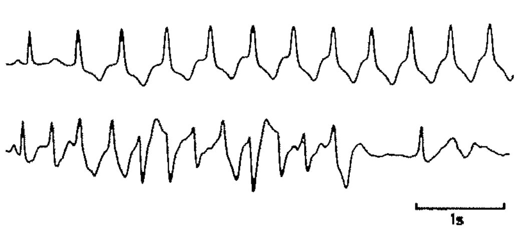

Figure 4 Ventricular tachycardia recorded during ambulatory electrocardiographic monitoring of the mother of the proband of family A. The ventricular tachycardia is at times multiform and irregular and at other times stable and monomorphic

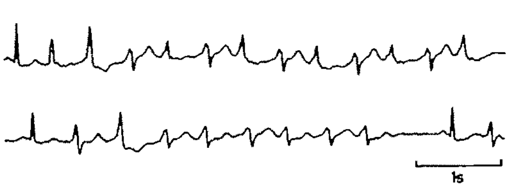

Figure 6 Ventricular tachycardia recorded during ambulatory electrocardiographic monitoring of the mother of the proband of family B. The ventricular tachycardia was non-sustained, at times bidirectional (middle trace), and at other times monomorphic (lower trace).

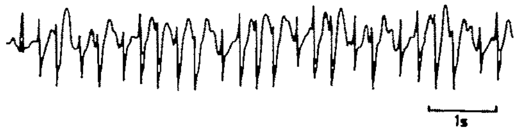

Figure 7 Ambulatory electrocardiographic recording from the proband of family C showing an irregular, wide QRS tachycardia, confirmed at electrophysiological study to be ventricular tachycardia.

showed a considerable improvement in ventricular function. After two years the patient remains symptom free on flecainide. Her chest *x* ray is normal and electrocardiographic monitoring shows sinus rhythm with frequent ventricular extrasystoles but without ventricular tachycardia.

The patient's mother first had palpitation 20 years ago and was treated with practolol for several years. At the time of investigation she was not taking medication. Her 24 hour electrocardiographic recording showed frequent, non-sustained, narrow QRS tachycardia occurring mainly at night. While this could be ventricular tachycardia, the precise nature of this arrhythmia has not been established because her symptoms do not warrant invasive investigation or treatment.

The mother's sister also gave a long history of palpitation. Her electrocardiogram recorded in 1970 showed non-sustained multiform ventricular tachycardia bearing a striking similarity to that of the proband. She had symptoms for 16 years despite treatment with quinidine. Recent reassessment showed frequent ventricular extrasystoles that continued after quinidine was stopped. Ventricular tachycardia was not present on 24 hour electrocardiographic monitoring. The resting electrocardiogram and cross sectional echocardiogram were normal. Treatment with flecainide initially reduced the ventricular ectopic activity but after some months her symptoms and the arrhythmia recurred. Other antiarrhythmic drug treatments are being investigated.

The maternal grandfather's family showed a strikingly high incidence of early death said to be due to heart disease but no further details are available (fig 1). The mother's cousins, both female, have also had arrhythmias. One cousin died suddenly at the age of 17 years and the other is alive and although she has symptoms she is not taking medication.

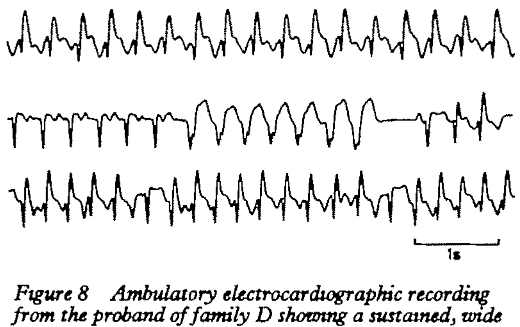

Figure 8 Ambulatory electrocardiographic recording from the proband of family D showing a sustained, wide QRS tachycardia with varying QRS configuration, confirmed at electrophysiological study to be ventricular tachycardia.

Discussion

THE ARRHYTHMIAS AND THEIR PATHOPHYSIOLOGY

Understanding of the pathophysiology and electrophysiology of ventricular tachycardia in children has been hampered by its rarity. The long QT syndrome and torsade de pointes are now widely recognised but, although it is tempting to consolidate new cases with others previously described, the growing trend to soften the diagnostic criteria of the long QT syndrome may inappropriately amalgamate diverse pathophysiological conditions. It may be better to use the term "abnormal repolarisation syndromes" to cover both the classic long QT syndromes and patients with normal QT intervals but with abnormal U waves, and to incorporate the possibility of abnormal repolarisation with a normal QT interval and normal U waves—a situation perhaps created by abnormally rapid repolarisation in parts of the heart, which produces pathological dispersion of repolarisation.

The cases of ventricular tachycardia presented are somewhat similar. All would satisfy even the most stringent definition of ventricular tachycardia. All occurred in young patients and in each there was evidence of a familial problem. Within each family there was a strikingly uniform type of arrhythmia. Yet, these interesting similarities are insufficient to establish a common electrophysiological or pathophysiological basis. The cases of ventricular tachycardia reported here are also recognisably different from the more common and apparently benign forms of repetitive monomorphic ventricular tachycardia seen in children without obvious heart disease.

Family A showed abnormal repolarisation with a normal QT interval but abnormal U waves. Since the original descriptions of the Jervell Lange-Nielsen[1] and Romano Ward[2 3] syndromes it has been apparent that other similar cases have variable inheritance or are sporadic[4] and that an apparently similar clinical picture can be seen with a normal QT interval.[5-7] Some patients in the latter group, like those in family A, have large, prominent, and prolonged U waves.[8 9] U waves probably reflect repolarisation of the Purkinje system[10] and abnormal U waves may signify abnormal repolarisation, which is the probable underlying abnormality in the classic "long QT syndrome".[4] There is no consensus on when the U wave is abnormal, either in height or duration. It has been suggested that U waves can be regarded as normal when they are up to 50% of the height of the T wave and that a U wave "approaching the height of the T wave" should be considered abnormal and should then be included in measurement of the QT interval.[10] The limits of normal QU duration are not known.

Family B also showed abnormal repolarisation. Though the multiform ventricular tachycardia and the abnormal U wave might indicate an underlying abnormality of repolarisation, we were unable to show dispersion of ventricular refractoriness and there was no response to β blockers. Multiform ventricular tachycardia and bidirectional ventricular tachycardia can coexist and both can also occur in the long QT syndrome.[11] Most of the few cases of bidirectional ventricular tachycardia reported in children have caused symptoms, with a high morbidity and mortality.[11-13] Coumel *et al* have described a rare type of catecholamine induced ventricular tachycardia, induced by exercise or isoprenaline infusion, that progresses through bidirectional tachycardia to ventricular fibrillation.[13]

There is no direct evidence of abnormal repolarisation in families C and D but the incessant nature of the arrhythmias precluded such analysis. Though it may seem that the ventricular tachycardia in these two families might be a consequence of myocardial disease, the ventricular impairment was mild and may equally have been a result of the arrhythmia.[14] Dilated cardiomyopathy may be familial and in some cases there is autosomal dominant inheritance.[15] Familial cases are heterogeneous but they do show a strikingly high incidence of arrhythmias, syncope, and sudden death.[16]

Familial ventricular tachycardia has also been reported in association with arrhythmogenic right ventricular dysplasia when almost all those affected are male,[17 18] in palmoplantar keratosis with right ventricular or biventricular disease,[19] in childhood periodic paralysis,[20] and in various neuromuscular diseases with cardiac involvement.[21]

GENETICS

In each of these four families the proband is a female who presented in adolescence. Furthermore, it is apparent from fig 1 that there is a preponderance of affected females. Although the type of arrhythmia within each family is consistent, it is inappropriate to pool the families for analysis because there are clear distinctions between them. In particular, family D is the only one in which there is obligate transmission of the gene from a male (I.6). In that male's sibship there were two early male deaths suggesting that in family D this may well be a simple autosomal dominant and the preponderance of females in the observed generation is a chance finding.

In the other families the female predominance may be no more than a chance observation. There are relatively few males and there is no evidence of an excess number of miscarriages to suggest a more severe form of the disease causing early loss of affected males. The small number of families and the likelihood of heterogeneity prevent formal segregation analysis but the possibility of some form of matrilineal transmission deserves examination in future family studies.

There are several disorders that preferentially affect females or are transmitted in the female line. In congenital myotonic dystrophy, some form of maternofetal interaction is assumed because the disorder is invariably inherited from the mother. Maternofetal transmission of an infectious agent is possible; $\mathrm{Hb_sAg}$ positive hepatitis was described as a familial disorder transmitted in the female line before it was recognised that the virus was transferred at delivery.[22] It has been suggested that familial ventricular tachycardia may result from familial transfer of neurotropic viruses causing selective damage of conducting tissue, but though this is theoretically possible there is no supportive evidence.[23]

Transmission in the female line is also characteristic of mitochondrial inheritance because mitochondria are derived almost exclusively from the ovum. There is now clear evidence that some cases of mitochondrial myopathy result from an abnormality in the mitochondrial genes, which are distinct from those of the nuclear genome. This mechanism of transmission is of potential relevance in view of the involvement of the conducting tissue in the Kearns-Sayre syndrome that has been shown to be associated with mitochondrial abnormality.[24] These mechanisms would result in preferential transmission in the female line but not in an exclusive involvement of female offspring. A further observation of possible relevance is the suggestion that various cardiac malformations are associated with a much greater recurrence risk in the offspring of affected females than of affected males.[25] No explanation for this excess is yet apparent.

Future studies of ventricular tachycardia should assess in further detail any relation between sex and the expression of transmission of a conduction defect. Clinicians should be aware of the need to inquire after, and where necessary to investigate, first degree relatives of individuals with ventricular tachycardia.

There is a clear need for more extensive family studies in ventricular tachycardia. The four families described in this report show that familial ventricular tachycardia is heterogeneous and that pooling of families is likely to be counterproductive, both to the delineation of the clinical phenotypes and to the possible localisation of the gene defects using DNA linkage studies.

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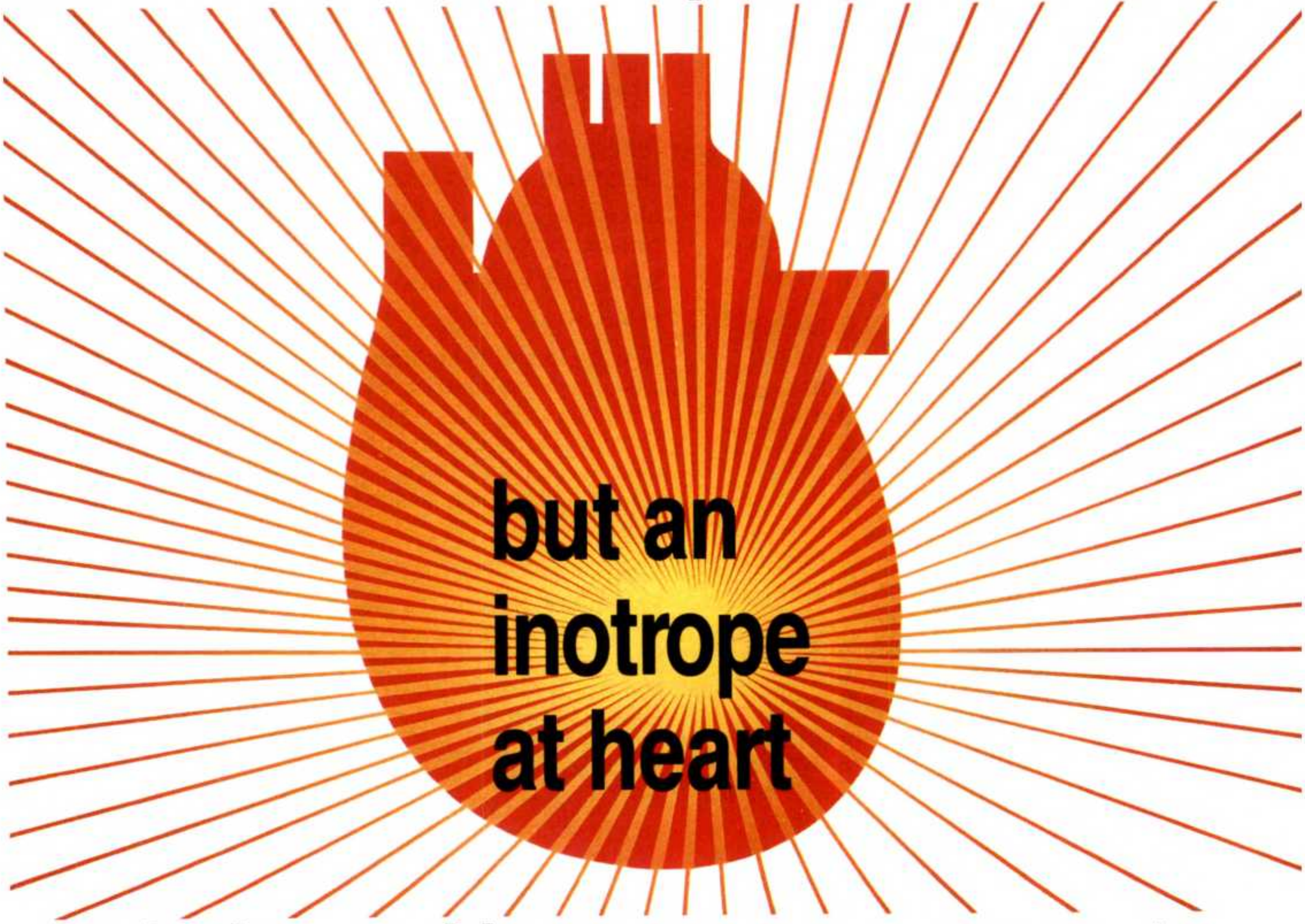

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Br Heart J 1990;63:175–7

Echocardiographic appearance of pulmonary artery stenosis

Jonathan W Swan, John B Chambers, Mark J Monaghan, Graham Jackson

Abstract

Colour flow Doppler mapping can show abnormalities of flow even when the echocardiographic image is equivocal. Routine echocardiography in two patients who were thought to have pulmonary valve stenosis and a ventricular septal defect initially appeared to be normal. Colour flow Doppler mapping, however, showed multiple flow aliasing within the pulmonary artery, approximately 1·5 cm downstream from the pulmonary valve. More detailed examination by cross sectional echocardiography showed a membrane at this level in both patients. It is possible that more cases of this uncommon anomaly will come to light with increasing use of Doppler techniques.

Cross sectional echocardiography provides an anatomical diagnosis in a wide variety of congenital and acquired cardiac lesions. The technique may provide technically poor images in some patients, however, and a morphological abnormality may not be obvious. In these situations, the spatial flow information provided by colour flow Doppler mapping may be diagnostic.[1] Supravalvar pulmonary artery stenosis is rare, but we have recently used colour flow Doppler mapping to diagnose two cases in which the cross sectional images were equivocal.

Case reports

CASE 1

A nineteen year old woman in whom valvar pulmonary stenosis had been diagnosed in infancy was seen for outpatient follow up. There was no history of maternal rubella and she had had a normal birth history and developmental milestones. On examination, there was mild bilateral ptosis, but no other neurological or physiognomic abnormality. The supine blood pressure was 120/85 mm Hg and the pulse rate was 64 beats/minute. The jugular venous pulse was normal and there was no parasternal impulse or abnormality of the apex beat. On auscultation there was a loud ejection systolic murmur, heard best at the left sternal edge in inspiration. The second sound was normal. The electrocardiogram showed sinus rhythm with no evidence of right ventricular hypertrophy and a mean frontal QRS axis of −40°. The chest x ray was normal.

CASE 2

A thirty one year old man presented with chest pain that was atypical of a cardiac origin. His developmental milestones had been normal, but a ventricular septal defect had been diagnosed in childhood. On examination, the supine blood pressure was 125/75 mm Hg and the pulse rate was 72 beats/minute. The jugular venous pressure was normal and there was no clinical evidence of right ventricular hypertrophy or left ventricular dilatation. On auscultation there was an ejection systolic murmur which was loudest at the left sternal border, but the second sound was normal. The electrocardiogram and chest x ray were normal.

ECHOCARDIOGRAPHY

Echocardiographic examination in both cases showed normal right and left ventricular function. There was no right ventricular hypertrophy and no evidence of intracardiac shunts. The cardiac valves were normal in appearance. Initial imaging of the right ventricular outflow tract and pulmonary artery also seemed normal. Colour flow Doppler mapping, however, showed a colour change indicating flow acceleration just beyond the pulmonary valve. This led to a constriction in flow within the main pulmonary artery 1·5 cm distal to the valve. Beyond this was a turbulent jet directed along the medial border of the artery (fig 1a). In the second case, there was additional reversed flow through the membrane in early diastole (fig 2a). More detailed examination by cross sectional echocardiography showed a membrane-like stenosis at this point in both cases (figs 1b and 2b). The peak velocity in the right ventricular outflow tract and proximal pulmonary artery, measured by pulsed Doppler, was 1·0 m/s in both cases. The peak pulmonary artery velocity, recorded by continuous wave Doppler, was 2·8 m/s in case 1 and 3·0 m/s in case 2, suggesting peak instantaneous gradients of around 30 mm Hg. No further investigation is planned in either patient.

Discussion

Our main purpose is to present the echocardiographic and Doppler ultrasound findings in this uncommon congenital anomaly. There are few reports of the cross sectional echocardiographic appearance of pulmonary artery stenosis and, to our knowledge, none of the Doppler ultrasound findings.

We showed several abnormalities within the pulmonary artery using colour flow Doppler mapping. Acceleration of flow began just

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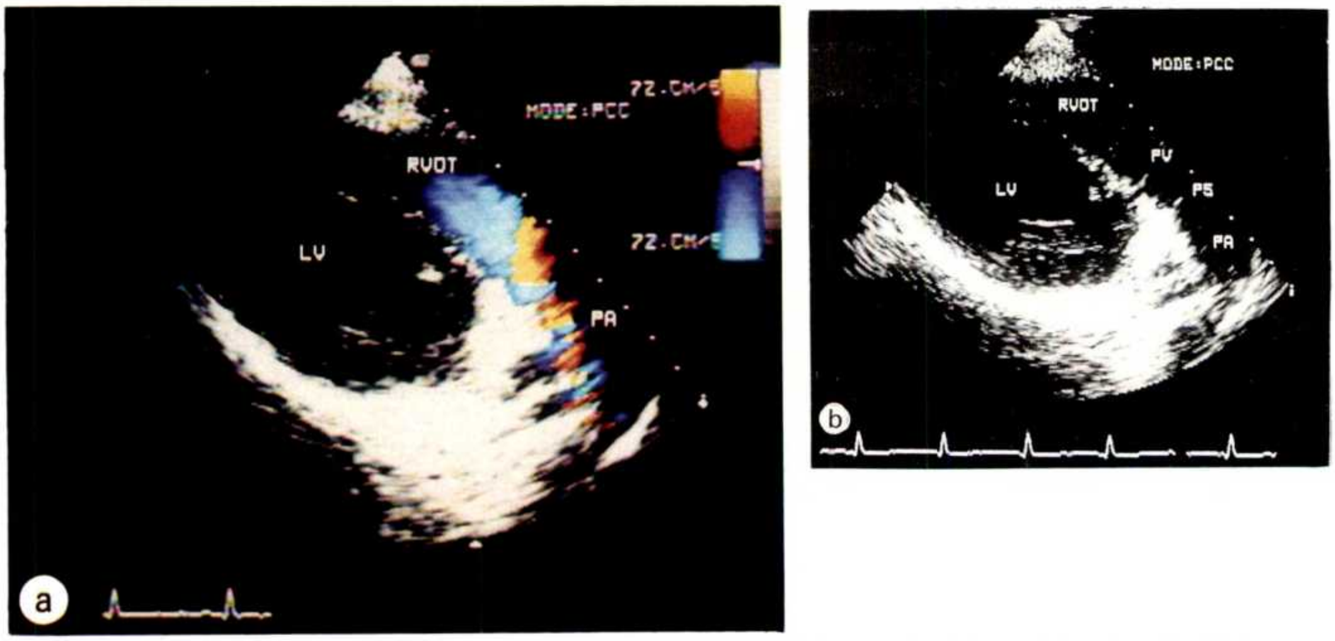

Figure 1 Echocardiographic appearance in case 1 with (a) and without (b) a superimposed colour flow map. A parasternal long axis view was used. The colour system was set at maximum packet size and minimum reject with an enhanced map and spatial filtering. (a) Flow acceleration can be seen immediately downstream from the pulmonary valve leading to a region of flow restriction at a point 1·5 cm from the valve. Beyond this is a high velocity jet, characterised by multiple mosaic aliasing, directed along the medial border of the pulmonary artery. (b) This shows the underlying anatomy corresponding to these regions of flow disturbance. LV, left ventricle; PA, pulmonary artery; PS, pulmonary artery stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract.

downstream from the pulmonary valve and led to a constriction in the cross sectional area available for flow at the point of the stenosis. Downstream from the stenosis was a fast turbulent jet, shown by multiple mosaic aliasing, which was directed along the medial wall of the pulmonary artery. These findings are similar to those reported for aortic coarctation where colour flow mapping may occasionally improve the detection rate.[2] In the present cases, the stenosis was not immediately obvious on cross sectional imaging and previous examinations had also failed to make the diagnosis. The unequivocal abnormality on colour flow mapping, however, drew attention to the region that required further more careful examination by cross sectional echocardiography.

The finding of early diastolic regurgitation across the membrane in one patient is interesting. The pressure drop was greatest at a point just distal to a membranous stenosis, beyond which blood lost momentum with a consequent recovery of static pressure.[3] We suggest that this pressure gradient beyond the membrane was the reason for transient flow reversal at the start of diastole.

Stenosis of the main or branch pulmonary arteries is uncommon; it is sometimes a result of maternal rubella.[4] A membrane is less common than an elongated stenosis and was seen in

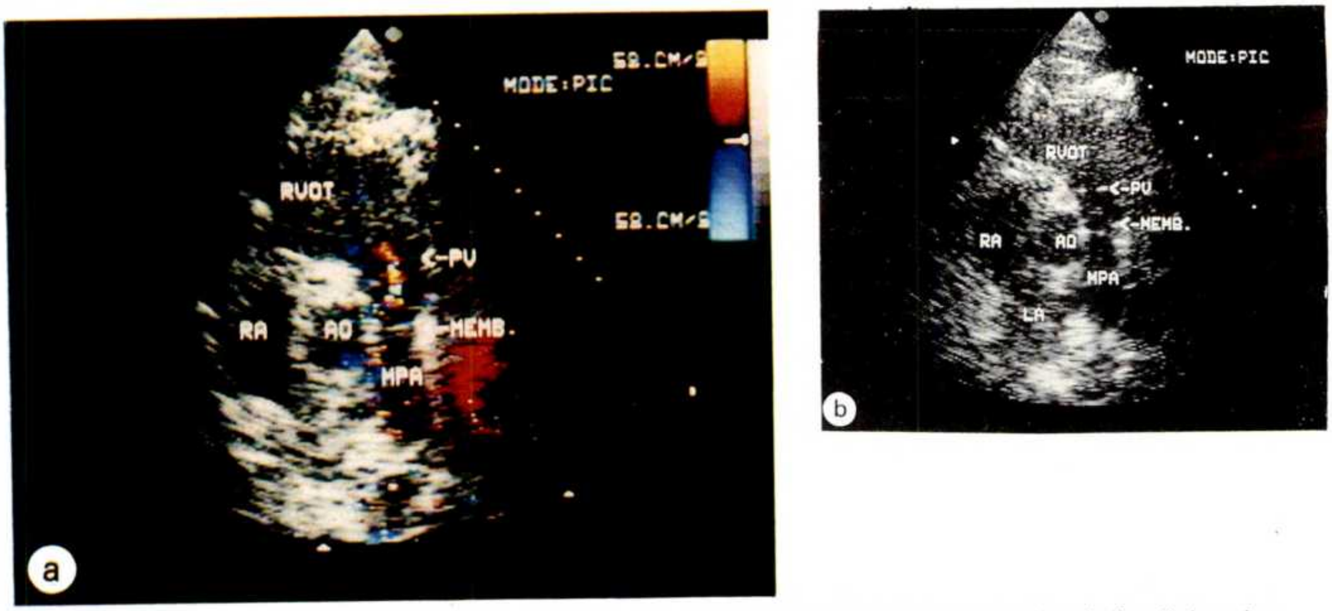

Figure 2 Echocardiographic appearance in case 2 with (a) and without (b) a superimposed colour flow map. (a) An early diastolic frame in a parasternal short axis view. The system was set as in fig 1a except that spatial filtering was not used. A short, narrow jet can be seen in the main pulmonary artery representing regurgitation of blood past the pulmonary artery membrane. (b) This shows the underlying anatomy. AO, aorta; memb, membrane; MPA, main pulmonary artery; PS, pulmonary artery stenosis; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract.

two of six patients in Franch and Gay's series in which the main pulmonary artery was affected.[5] Few long term studies have been undertaken, but it seems that gradients across stenoses in the main pulmonary artery change little over periods of up to 12 years and the prognosis is good in the absence of other associated cardiac anomalies.[6]

Colour flow Doppler is effectively a cross sectional version of pulsed Doppler. Velocity and directional data are gathered at multiple depths down the scan lines of an image sector and then superimposed on the cross sectional image. It therefore screens rapidly for disturbances of flow that may not always be associated with anatomical abnormalities. Furthermore, the detection and localisation of such flow disturbances may be time consuming and of limited accuracy when continuous wave and conventional pulsed Doppler are used. Attention was first directed to the main pulmonary artery in these cases by the unequivocal abnormality on colour flow Doppler mapping. It thus considerably simplified the examination, enabling pulmonary artery stenosis to be diagnosed for the first time in these patients. It is possible that pulmonary artery stenosis is underdiagnosed and that more cases may come to light with the increasing availability and use of Doppler ultrasound techniques.

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Addendum

Since preparing this paper we have demonstrated three further cases of membranous pulmonary artery stenosis, suggesting that it may be more common than previously thought.

Br Heart J 1990;63:178–9

CASE REPORTS

Percutaneous transluminal coronary angioplasty with cardiopulmonary bypass for stenosis of the most proximal part of the left anterior descending coronary artery

Osamu Ueda, Kyoji Kohchi, Nobuhiko Koga

Abstract

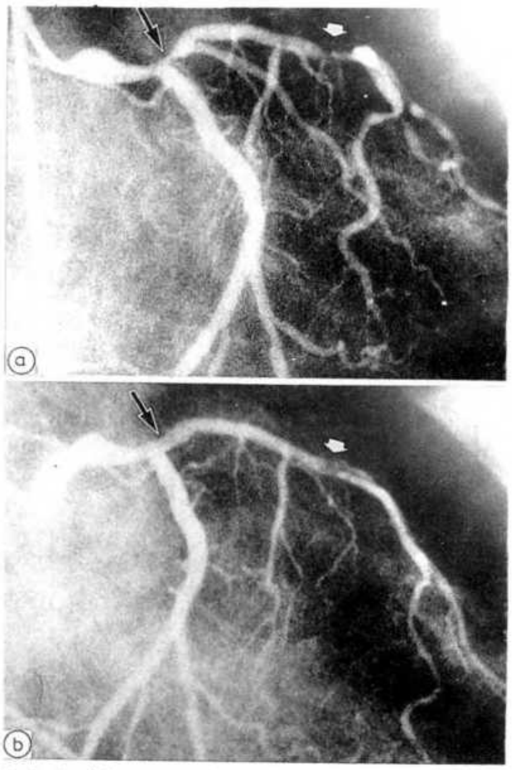
An 85 year old man with unstable angina pectoris was treated successfully with percutaneous transluminal coronary angioplasty supported by cardiopulmonary bypass and intra-aortic balloon pumping. Coronary angiography had shown stenoses in both the left main stem and left anterior descending coronary arteries. Drug treatment had been ineffective and he was too old for coronary arterial bypass grafting.

Although percutaneous transluminal coronary angioplasty for stenosis of the left main stem coronary artery without adequate protection of other arteries has been attempted in an emergency and electively,[1-3] such a lesion is regarded by some as an absolute contraindiction to elective coronary angioplasty.[4 5] Vogel and Phillips *et al* reported using cardiopulmonary bypass for risky coronary angioplasty.[6 7] We report successful emergency angioplasty in a high risk patient who was supported by cardiopulmonary bypass and intra-aortic balloon pumping.

Case report

An 85 year old man was brought by ambulance to our hospital with chest pain that was refractory to sublingual glyceryl trinitrate. He had a four year history of stable effort angina. On admission, his blood pressure was 152/72 mm Hg, the pulse rate was 66 beats per minute and regular, the lungs were clear, and cardiac auscultation showed no abnormal findings. An electrocardiogram showed sinus rhythm with no clinically significant ST-T change. The attack disappeared after intravenous administration of 5 mg of isosorbide dinitrate. His attacks of angina at rest continued in hospital despite treatment with maximal doses of nitrates and calcium channel blockers. The electrocardiogram during anginal attacks showed slight ST depression in leads V3 to V5. Coronary arteriography on the fifth hospital day showed a severe stenosis (90% of the diameter) in the most proximal part of the left anterior descending coronary artery that extended to the left main stem coronary artery and another severe stenosis (90%) in the middle left anterior descending coronary artery (fig 1a).

We thought that the patient was too old for coronary arterial bypass grafting. Coronary angioplasty was considered to be so risky that we decided to use cardiopulmonary bypass and intra-aortic balloon pumping during angioplasty. We attempted coronary angioplasty on the sixth hospital day. The patient gave his informed consent. The balloon for intra-aortic balloon pumping was inserted from the right femoral artery. After general anaesthesia with nitrous oxide, the cannulas for cardiopulmonary bypass were introduced into the left femoral artery and the left femoral vein by surgical exposure. Angioplasty was performed via the brachial approach with a 2·5 mm



Selective left coronary cineangiograms made (a) before and (b) after percutaneous transluminal coronary angioplasty. The black arrow head and arrow indicate proximal and distal 90% stenosis respectively; both were successfully treated by angioplasty supported by bypass.

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diameter balloon catheter. When the balloon was across the lesion in the most proximal part of the left anterior descending coronary artery it was inflated three times for 30 to 60 seconds at a pressure of 8 atmospheres. Because the systemic blood pressure fell below 70 mm Hg despite intra-aortic balloon pumping during the first inflation, cardiopulmonary bypass was used to give a blood flow of 2 l/min. Blood pressure was soon restored. The balloon was inflated once for 120 s at 7 atmospheres when it lay across the lesion in the middle left anterior descending coronary artery. The lesion in the most proximal part of the left anterior descending coronary artery was not sufficiently dilated, so a larger balloon (3 mm diameter) catheter was used and inflated twice for 120 seconds at a maximum pressure of 5 atmospheres.

The diameter of both stenotic regions was increased from 10% to 50% by dilatation (fig 1a and fig 1b). Although there was a minor dissection in the mid left anterior descending coronary artery, there was no occlusion of the artery during the half an hour observation after dilatation. These procedures were performed uneventfully. After angioplasty, angina was completely controlled by medicine and the patient was discharged a month later.

Discussion

Our patient had two severe stenoses (> 90%) in the left anterior descending coronary artery, and a successful dilatation of only one stenotic region might have relieved the symptoms. To reach the stenosis in the mid left anterior descending coronary artery we had to pass the balloon catheter through the most proximal stenosis. Dilatation of either stenosis was very risky. Because angioplasty of the most proximal lesion required the support of cardiopulmonary bypass and intra-aortic balloon pumping we decided to attempt both stenoses.

We did consider whether the left circumflex coronary artery should have been protected with an additional guide wire, because the most proximal stenosis extended to the left main coronary artery. The stenosis of the left main coronary artery itself was not so severe, however, and we therefore considered that the left circumflex coronary artery was unlikely to become occluded.

We thank Dr H Okazaki, Dr T Baba, Dr H Ohteki, and Professor T Itoh for support and advice

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Br Heart J 1990;63:180–2

Origin of the left coronary artery from the right pulmonary artery and ventricular septal defect in a child of a mother with raised plasma phenylalanine concentrations throughout pregnancy

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Abstract

A child with anomalous origin of the left coronary artery from the right pulmonary artery, ventricular septal defect, fetal growth retardation, and facial abnormalities was born to a woman in whom plasma phenylalanine concentrations had been raised throughout pregnancy. The cardiac abnormalities were diagnosed by angiography when the child was eight months old. The anomalous coronary artery was imaged in a subsequent echocardiogram. Development retardation was caused by maternal phenylketonuria, which may also have been responsible for the development of the ventricular septal defect and the coronary anomaly. If dietary treatment of the mother had been started before pregnancy damage to the child might have been prevented.

Anomalous origin of the left coronary artery from the pulmonary artery as an isolated lesion usually presents as myocardial ischaemia.[1] Haemodynamic features caused by associated intracardiac lesions may obscure the clinical features of the coronary artery anomaly. Reports of children with this anomaly and an associated ventricular septal defect show that the coronary anomaly was not detected until operative closure of the ventricular septal defect was followed by a fatal outcome or until signs of myocardial ischaemia developed in children in whom the ventricular septal defect had spontaneously become smaller.

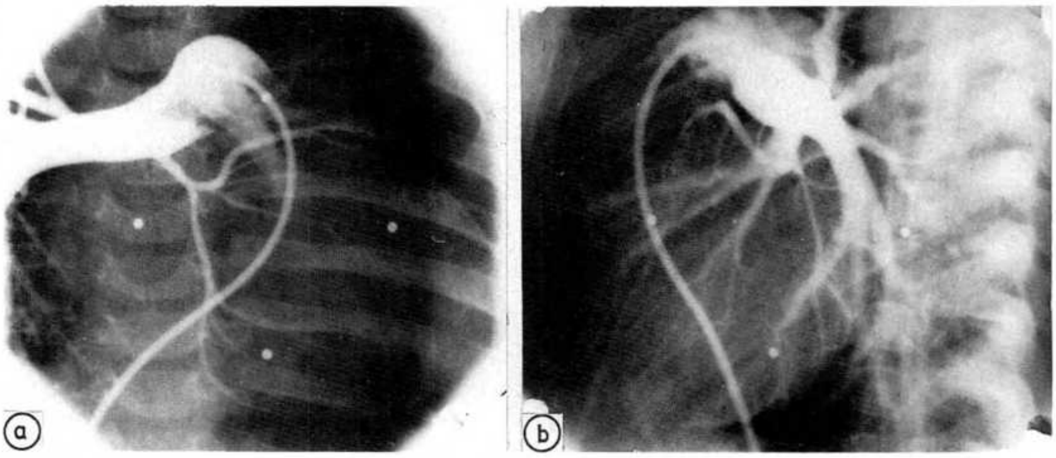
We report on one infant in whom the anomaly—origin of the left coronary artery from the right pulmonary artery—was diagnosed before operation. We know of five reports of this rare condition.[2-6] The mother of the patient we describe was found to have raised plasma concentrations of phenylalanine after delivery.

Case report

The female infant was delivered by caesarean section at 36 weeks' gestation because of slowing of the fetal heart rate. An ultrasonic evaluation in week 15 of pregnancy had shown growth retardation of the fetus. Apart from this, pregnancy had been uneventful. There was no history of congenital heart disease in the family. At birth the child was small for dates (birth weight of 1460 g), microcephalic, and showed several signs of facial dysplasia consistent with the high maternal plasma concentration of phenylalanine (2·46–3·06 mmol/l) measured soon after delivery. In the next few weeks a grade 3/6 continuous systolic murmur was audible along the infant's left sternal border. A low frequency mid-diastolic murmur could be heard at the apex of the heart. The intensity of the second part of the second heart sound was increased. The liver was slightly enlarged, there was no cyanosis, and the peripheral pulses were normal. Follow up chest *x* rays and electrocardiograms showed cardiomegaly, increased pulmonary vascularity, and signs of double ventricular hypertrophy without T wave inversion or ST segment or T wave anomalies. Echocardiographic examination showed a ventricular septal defect (diameter 4 mm), left and right ventricular and septal hypertrophy, and slight atrial enlargement. The shortening fraction and ejection fraction, calculated by means of M mode echocardiography, were within normal limits. During the ensuing months there was no clinical or electrocardiographic evidence of ischaemia of the myocardium.

When the child was eight months old cardiac catheterisation was performed. She was small (6·1 kg)—in the third percentile for weight at eight months. Cardiac catheterisation confirmed the diagnosis of ventricular septal defect. Pulmonary artery pressure was raised because the left and right ventricular systolic pressures were almost equal. The calculated left to right shunt was 57% and pulmonary vascular resistance was within normal limits. Cineangiography provided the complete diagnosis. Injection into the left ventricle showed normal contractility of this chamber, no mitral valve incompetence, and a ventricular septal defect in the typical high location. After left ventricular contraction the aortic root, the right coronary artery, and a relatively large conal branch were seen without any evidence of left coronary artery filling. Injection into the right ventricle and selective angiography of the right pulmonary artery showed the origin of the anomalous left coronary artery on the right pulmonary artery approximately 1 cm away from the bifurcation (fig 1). The anomalous artery ran below and behind the pulmonary trunk. Then it divided. One of the branches

Figure 1 Angiograms after injection of contrast into the right pulmonary artery showing the anomalous origin of the left coronary artery from the right pulmonary artery in (a) frontal and (b) lateral views.

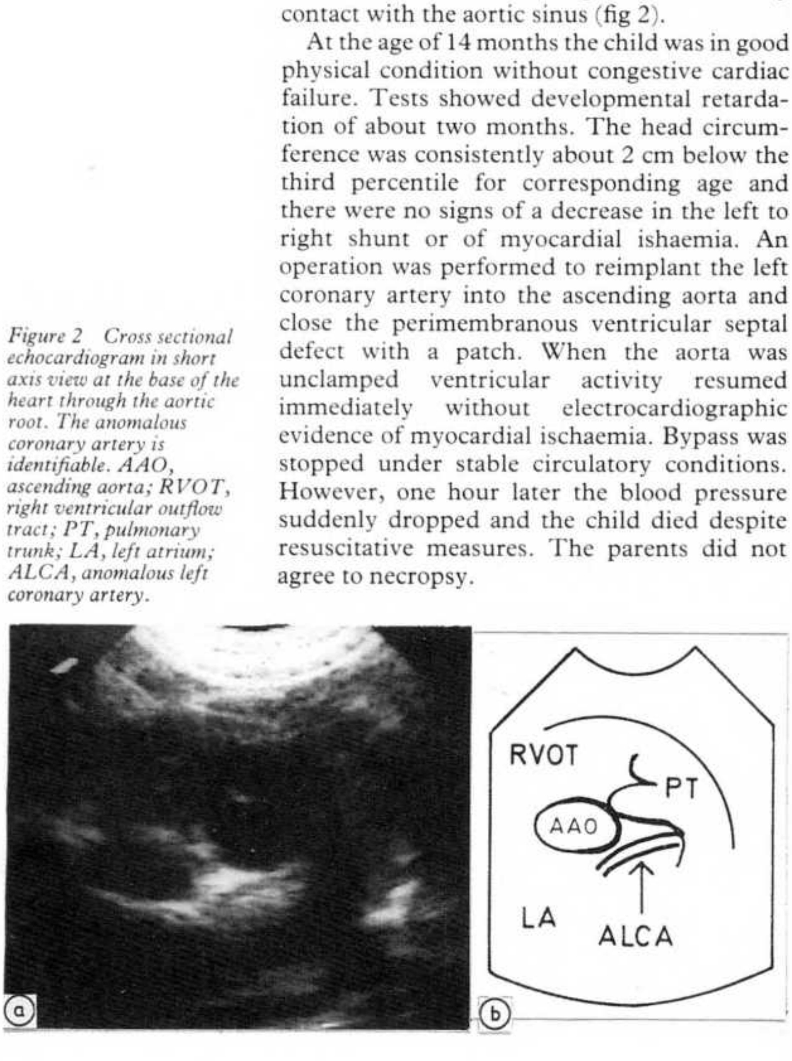


followed the usual course of the anterior descending coronary artery and the other that of the circumflex coronary artery. No collaterals were seen between the left and right coronary artery system.

This coronary anomaly was examined by cross sectional echocardiographic study through the aortic root. In the short axis view no coronary artery ostium was seen in the left aortic sinus. Slight cranial angulation of the transducer showed the anomalous coronary artery following a straight course below and to the left behind the ascending aorta without any contact with the aortic sinus (fig 2).

At the age of 14 months the child was in good physical condition without congestive cardiac failure. Tests showed developmental retardation of about two months. The head circumference was consistently about 2 cm below the third percentile for corresponding age and there were no signs of a decrease in the left to right shunt or of myocardial ishaemia. An operation was performed to reimplant the left coronary artery into the ascending aorta and close the perimembranous ventricular septal defect with a patch. When the aorta was unclamped ventricular activity resumed immediately without electrocardiographic evidence of myocardial ischaemia. Bypass was stopped under stable circulatory conditions. However, one hour later the blood pressure suddenly dropped and the child died despite resuscitative measures. The parents did not agree to necropsy.

Figure 2 Cross sectional echocardiogram in short axis view at the base of the heart through the aortic root. The anomalous coronary artery is identifiable. AAO, ascending aorta; RVOT, right ventricular outflow tract; PT, pulmonary trunk; LA, left atrium; ALCA, anomalous left coronary artery.



Discussion

The cardiac malformation in this infant consisted of an anomalous origin of the left coronary artery from the right pulmonary artery and a ventricular septal defect. These anomalies, the growth retardation before and after birth, the microcephaly, and the abnormal facial appearance of this newborn infant suggested that maternal phenylketonuria might be the common cause.[7,8] Grossly raised maternal plasma concentrations of phenylalanine soon after delivery confirmed the diagnosis. If maternal dietary treatment had been started before conception[9,10] this child might not have been damaged.

To date there have been five reports of origin of the left coronary artery from the right branch of the pulmonary artery.[2-6] In our patient the left coronary artery originated at exactly the same site as discussed by other workers—that is 0·5–1 cm distal to the bifurcation from the right pulmonary artery. In the two cases reported by Doty *et al* and Hamilton *et al* there were no associated cardiac lesions.[2,3] Surgical correction was successful by anastomosis of the left coronary artery to the right subclavian artery in one child[2] and by implantation of the anomalous coronary artery into the aorta in the other.[3] Haemodynamic changes resulting from an associated ventricular septal defect obscured the clinical features of the coronary anomaly in the cases reported by Rao *et al* and by Wilcox *et al.*[5,6] Both children died immediately after surgical closure of the ventricular septal defect. Necropsy showed the associated anomalous origin of the left coronary artery from the right pulmonary artery. The haemodynamic basis for this fatal outcome was the drop in pulmonary arterial pressure when the ventricular septal defect was closed. This caused a fall in coronary artery perfusion followed by myocardial ischaemia and death. The same mechanism was seen in two children reported by Pinsky *et al*[11]: spontaneous reduction in the size of a ventricular septal defect resulted in myocardial ischaemia and infarction. Earlier identification and repair of the anatomical abnormality could have prevented the irreversible myocardial damage in all of these reported patients.

The associated coronary anomaly could have been identified in our patient during cardiac catheterisation at the age of eight months. Left ventricular angiography clearly showed the right coronary artery but not the left coronary artery. This led to the suspicion of a coronary artery anomaly, which was confirmed and identified by right ventricular and right pulmonary angiography. A cross sectional echocardiogram after cardiac catheterisation also identified the anomalous coronary artery. So the identification of anomalous origin of the left coronary from the pulmonary artery in patients with ventricular septal defect would be increased if every child with a ventricular septal defect was examined by cross sectional echocardiography to assess the origin of the coronary arteries from the aortic root, ventricular cineangiography to image the arrangement of the coronary arteries, and if necessary by aortography.

In addition, we have started a routine assessment of coronary arteries by echocardiography in every child in our outpatient clinic. We are, however, aware that rare anomalies such as an origin of an accessory coronary artery from the pulmonary artery[12] or origin of the anterior branch of the left coronary artery from the pulmonary artery[13] will not be excluded by this method.

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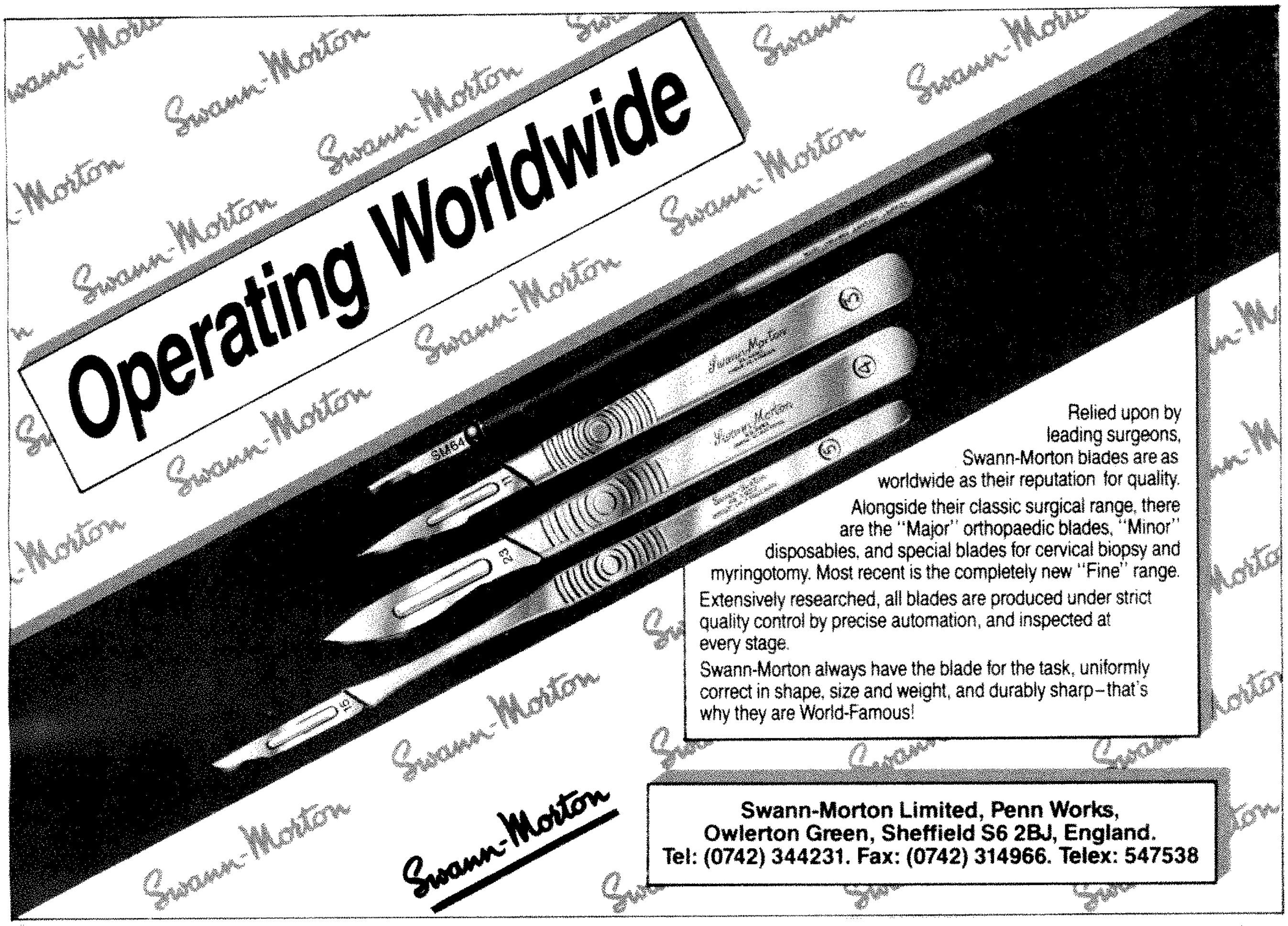

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Br Heart J 1990;**63**:183–5

Thrombosed saccular aneurysm of a sinus of Valsalva: unusual cause of a mediastinal mass

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Abstract

A 33 year old man presented with a short history of slight fever and chest pain that was worse on inspiration. An electrocardiogram was consistent with pericarditis. Chest radiography, echocardiography, and computed tomography suggested the presence of a mediastinal tumour. At operation the mass was found to be attached to the right sinus of Valsalva and proved to be a large saccular aneurysm full of laminated thrombus.

Aneurysms of sinus of Valsalva often remain undiagnosed until they rupture, usually into the right ventricle or atrium.[1] Such aneurysms may also present as obstruction of the right ventricular outflow tract,[2] aortic incompetence,[3] tricuspid stenosis and incompetence,[4] coronary artery compression,[5] and conduction abnormalities.[6] We describe a patient in whom there was evidence of a mediastinal mass. This proved to be a thrombosed saccular aneurysm originating from the right sinus of Valsalva.

Case report

33 year old, previously healthy, non-smoking, cardiology registrar referred himself for an electrocardiogram because of a 2 day history of fever and pain behind the sternum and in the right shoulder that was worse on inspiration. The electrocardiogram showed concave upwards elevation of the ST segment in the inferior and anterolateral leads suggestive of pericarditis. On examination he looked well but had a temperature of 37·8°C. His pulse was 70 beats/min, regular, and of normal character and volume. Blood pressure was 110/70 mm Hg. The jugular venous pressure was normal as was precordial palpation. Heart sounds were normal and there were no murmurs or rubs. The lungs were clear and the rest of the examination was unremarkable.

A posteroanterior chest radiograph showed an abnormal prominence of the right cardiac border and a lateral film showed an abnormal rounded shadow superimposed on the heart (fig 1). A chest radiograph performed 5 years before, which we were unable to obtain for comparison, had been reported as normal. An echocardiogram showed a large rounded echodense mass adjacent to the aortic root compressing the right atrium (figure 2a). A small rounded echo-free space of uncertain cause was noted within the mass. A small amount of pericardial fluid was seen. The aortic root and valve seemed to be normal. The rest of the examination, including Doppler examination

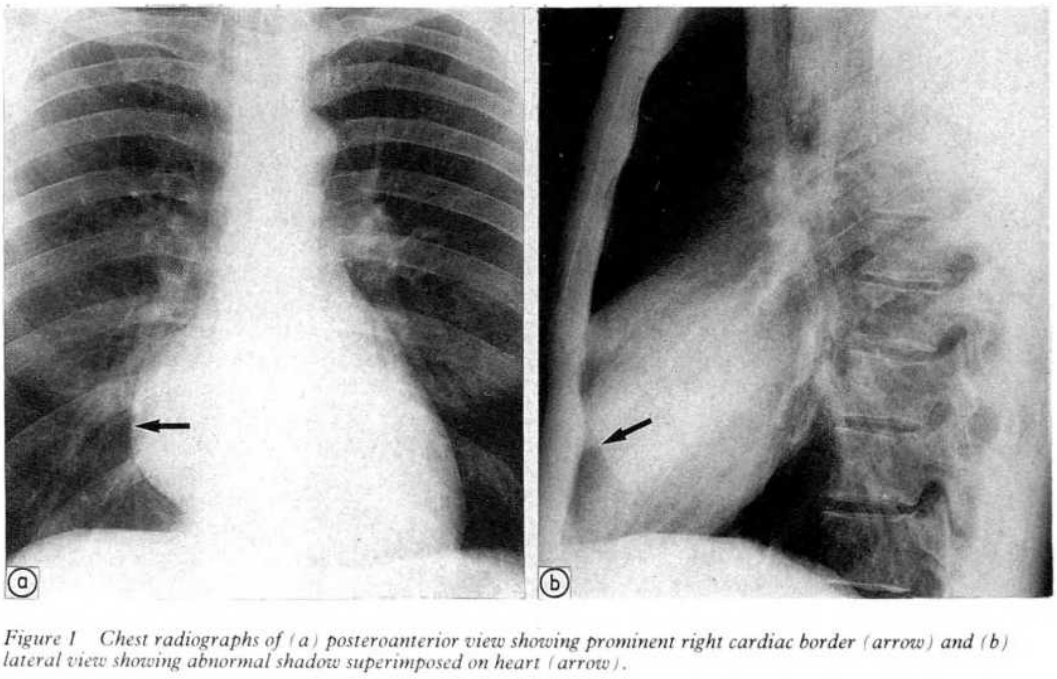

Figure 1 Chest radiographs of (a) posteroanterior view showing prominent right cardiac border (arrow) and (b) lateral view showing abnormal shadow superimposed on heart (arrow).

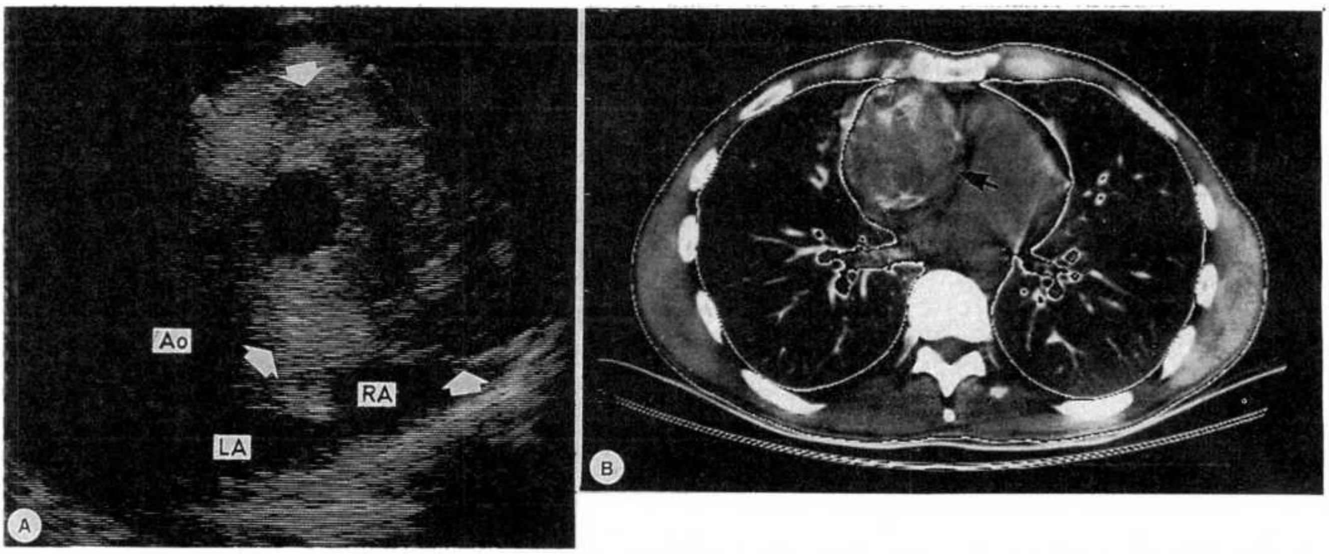

Figure 2 (a) Cross sectional echocardiogram: oblique scan from second right intercostal space showing a mass (arrows) compressing the right atrium. A rounded echo-free space is seen at one pole. Ao, aorta; LA, left atrium; RA, right atrium. (b) Unenhanced computed tomogram showing the mass (arrow) composed of a mixture of soft tissue and water densities with some calcified areas.

of all cardiac valves, was normal. Laboratory investigations showed a normal full blood count, erythrocyte sedimentation rate, blood urea, creatinine, electrolytes, liver function tests, and immunoglobulin concentrations.

A computed tomogram showed a rounded mass indenting the right side of the heart. It showed a mixture of soft tissue and water densities with several calcified areas (figure 2b). Contrast injection caused considerable enhancement of the nodule on the medial wall of the mass and the margins of the lesion became better defined. A fatty plane seemed to separate most of the mass from the adjacent aortic root and right heart structures. A germ cell tumour was considered to be the most likely diagnosis.

The mass was removed surgically 4 days after presentation.

OPERATIVE FINDINGS

The mass was situated subepicardially in the atrioventricular groove between the right atrial appendage, aortic root, and right ventricular outflow tract and measured 8 cm across at its widest point. It seemed to be well encapsulated and was hard and smooth. There was slight pericardial inflammation. The mass was dissected free under cardiopulmonary bypass. It was attached by a 2 cm diameter pedicle to the right sinus of Valsalva immediately adjacent to the origin of the right coronary artery, which was rudimentary and was unavoidably opened during removal of the mass. A small white plaque resembling atheroma was noted on the wall of the coronary artery. The left coronary artery, which gave rise to a large dominant circumflex vessel, seemed to be normal as did the remainder of the aorta.

PATHOLOGICAL FINDINGS

A 0·5 cm diameter hole in the wall of the mass, where it had been attached to the aorta, exuded blood on pressure. Transection showed that the mass had a thin, partly calcified wall and was largely full of laminated thrombus. The appearance suggested a saccular aneurysm. Histological examination showed that the wall was made up of fibrous tissue and smooth muscle with only a little elastic tissue. There was an extensive band of chronic inflammation with infiltration by lymphocytes and plasma cells. Numerous thick-walled blood vessels were seen in this band. There was no evidence of neoplasia.

POSTOPERATIVE COURSE

The patient's recovery was uneventful and he returned to work after two months. Serological tests for syphilis were negative and random serum cholesterol, measured four months after operation, was 4·0 mmol/l.

Discussion

Aneurysms arising from a sinus of Valsalva are uncommon and are thought to be most commonly mycotic, arising as a complication of infective endocarditis, or congenital in origin.[1] Other causes include syphilis, tuberculosis, Marfan and Ehlers-Danlos syndromes, trauma, and other disorders causing aortitis such as ankylosing spondylitis.

The aetiology in the present case is uncertain. Congenital aneurysms usually arise from the lower part of an aortic sinus and enlarge downwards within the heart rather than extend outwards into the pericardial cavity.[7] Mycotic aneurysms are typically saccular but there was no evidence of an infective cause in the present case. The inflammation seen in the wall of the aneurysm was not accompanied by macroscopic evidence of a more widespread aortitis and may have been a secondary development. Whatever the cause it is remarkable that the aneurysm had attained such a size without rupturing, particularly as it lay on the surface of the heart.

Cross sectional echocardiography was useful in the diagnosis of unruptured aneurysms of a sinus of Valsalva[8] and computed tomography was considered to be the primary means of distinguishing between para-aortic masses and saccular aortic aneurysms although this distinction is difficult when an aneurysm is completely filled with thrombus.[9] Both investigations were misleading in the present case because such a thrombus was present. In retrospect the echo-free space shown by echocardiography and the enhanced nodule seen on the computed tomogram probably both represented a small lumen in the aneurysm adjacent to its pedicle. Further investigation by aortic angiography might have suggested the correct diagnosis. The importance of angiographic studies of the right and left heart in cases of unusual anterior mediastinal masses that may arise from the heart has been emphasised[10] but these were not considered to be indicated in our patient because the non-invasive investigations suggested that the mass was a solid tumour.

This case shows that the possibility of a thrombosed vascular aneurysm shold be considered in the differential diagnosis of an apparently solid mediastinal mass.

We thank Dr D S Reid for allowing us to report on a patient under his care.

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Br Heart J 1990;**63**:186

Pulmonary oedema with shock induced by hydrochlorothiazide: a rare side effect mimicking myocardial infarction

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Abstract

The case of a 68 year old man in whom hydrochlorothiazide induced pulmonary oedema with hypovolaemic shock is presented. The condition was misdiagnosed as myocardial infarction until an early echocardiogram excluded a cardiac cause. The diagnosis was confirmed by an oral challenge.

Case report

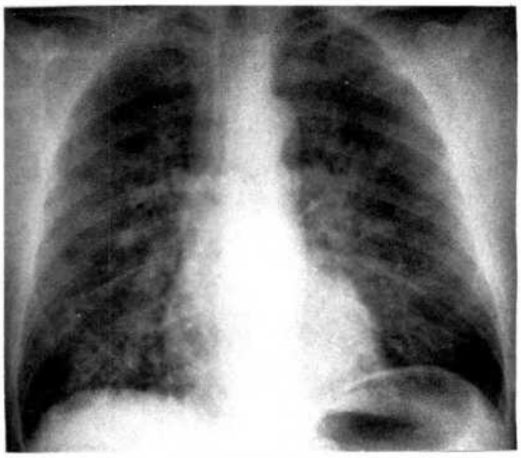
A 68 year old man with a previous myocardial infarction was admitted to hospital because of sudden severe dyspnoea, chest tightness, dizziness, and vomiting. He did not recollect taking any drugs. At arrival he was dyspnoeic, cyanotic, and sweating. Blood pressure was 60 mm Hg systolic, pulse 85, and temperature 36·2°C. Fine crepitations were heard bilaterally. Chest *x* ray indicated pulmonary oedema (figure) and the electrocardiogram showed sinus rhythm with widespread ST depressions. Arterial blood partial pressures were po_2 6·7 kPa and pco_2 3·5 kPa and the pH was 7·33.

Fibrinolytic treatment was considered but echocardiography showed good contraction of the left ventricle with signs of hypovolaemia. Treatment with albumin and saline was started; central venous pressure rose from 7 to 12 cm H_2O and the haematocrit fell from 0·59 to 0·47. Blood pressure became normal within 90 minutes.

In the next few days the electrocardiogram and serum concentrations of creatine kinase were normal whereas low grade fever, leucocytosis, and slight generalised oedema were seen. Chest *x* ray showed increasing infiltration followed by complete resolution. The patient was discharged but one month later he was readmitted with identical symptoms. This time he remembered taking hydrochlorothiazide (25 mg) for swollen ankles; earlier he had taken hydrochlorothiazide for two years because of hypertension. He recovered completely on saline alone. No paraprotein was found; eosinophil count, immunoglobulin E, Cl esterase inhibitor, radioallergosorbenttest, and histamine liberation from basophils exposed to hydrochlorothiazide were normal. The patient consented to an oral challenge with hydrochlorothiazide (12·5 mg) and 30 minutes after this dose symptoms developed.

Discussion

We found 11 published reports of shock and non-cardiogenic pulmonary oedema associated with hydrochlorothiazide.[1-10] The full-blown syndrome is only seen when treatment with hydrochlorothiazide is resumed after a long interval. No other thiazide diuretics seem to be incriminated in any of the cases. Our case seems to be the first report of challenge with hydrochlorothiazide as the only active compound; one other case was challenged with a combination of hydrochlorothiazide and triamterene.[4]



Chest x ray taken on admission showing bilateral pulmonary oedema.

An immunological pathogenesis has been suspected but test results have been equivocal; in our case we found no evidence of a classic type 1 mechanism. We regard both the pulmonary changes and hypovolaemia to be caused by extravasation owing to increased capillary permeability as in the systemic capillary leak syndrome,[11] but with the pulmonary vasculature being more sensitive.

In most cases the syndrome was initially misdiagnosed and one case died.[4] In our patient echocardiographic examination made prompt and adequate treatment possible.

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Br Heart J 1990;**63**:187–8

Absence of the aortic valve cusps with mitral atresia, normal left ventricle, and intact ventricular septum

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Abstract

A case of a previously unreported anomaly is presented in which absence of the aortic valve cusps, mitral atresia, a normal left ventricle, and an intact ventricular septum were diagnosed by cross sectional echocardiography. The development of a normal left ventricle, rather than the hypoplastic ventricle usually associated with mitral atresia, is explained by filling of the ventricular cavity via the regurgitant aortic valve.

Absence of the aortic valve cusps with a normal aortic root is a very rare anomaly. To our knowledge only three cases have been reported.[1-3] A hypoplastic left ventricle was found in all three cases; and in two there was a double outlet right ventricle. One case was diagnosed in life by cross sectional echocardiography. This report describes a case of absence of the aortic valve cusps with a normal left ventricle, mitral atresia, and enlarged ascending aorta that was diagnosed by cross sectional echocardiography and confirmed at necropsy.

Absence of the aortic valve cusps in association with a normal left ventricle has not previously been reported.

Case report

A baby weighing 3·5 kg was admitted to hospital when he was 12 hours old because of respiratory distress. He was the first son of healthy parents. Pregnancy was uneventful and he was delivered by caesarean section. Apgar scores at 1 minute and 10 minutes were 5 and 10 respectively.

On admission the baby had mild respiratory distress (60 breaths/min), cyanosis, and a heart rate of 160 beats/min. The axillary and femoral pulses were normal. He had a systolic-diastolic murmur that was heard best at the left upper sternal edge. Blood pressure was 70/40 mm Hg. The liver was not enlarged. A chest *x* ray showed cardiomegaly with dilatation of the right atrium and ascending aorta. The lung fields were normal. The electrocardiogram showed a QRS axis at −50 with left ventricular hypertrophy and alteration of repolarisation. Cross sectional echocardiography showed left ventricular enlargement with an increase in wall thickness and immobile papillary muscles. The ascending aorta was very dilated (1·4 cm in diameter) and the aortic valve cusps could not be found (fig 1). The pulmonary trunk was dilated with a dysplastic pulmonary valve. Saline was injected through a catheter inserted into the aortic arch via the umbilical artery and bubbles passed to the left ventricle.

The patient became increasingly ill and died when he was 24 hours old. The necropsy showed the following: the heart had a normal atrial arrangement; the pulmonary veins drained normally into the left atrium and the foramen ovalis was patent. The mitral valve was atretic with an imperforate valve membrane and a concordant atrioventricular connection but papillary muscles and chordae were present (figure 2a). The three aortic valve cusps were absent (figure 2b) but the coronary sinuses were normal although the aortic root was small. The size of the left ventricle was normal for the age of the patient. The ascending aorta was dilated and a ductus arteriosus was present. The pulmonary valve had three cusps, each showing some myxoid dysplasia.

Discussion

Patients who have situs solitus, two ventricles, a concordant ventriculoarterial connection, and atresia of the left atrioventricular valve usually have a normal aortic valve and a ventricular septal defect.[4-7] Mitral atresia is caused by an imperforate valve membrane at

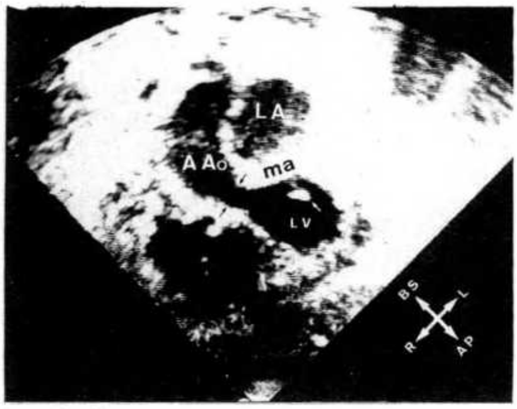

Figure 1 Cross sectional echocardiogram in subcostal long axis view showing a left ventricle with a cavity of normal size but with increased wall thickness. The ascending aorta was dilated and the aortic ring was small. The aortic valves were not seen in systole or in diastole. LV, left ventricle; A Ao, ascending aorta; LA, left atrium; ma, atretic mitral valve. The black arrow indicates the valve ring and the white arrows the papillary muscle. AP, apex; BS, base.

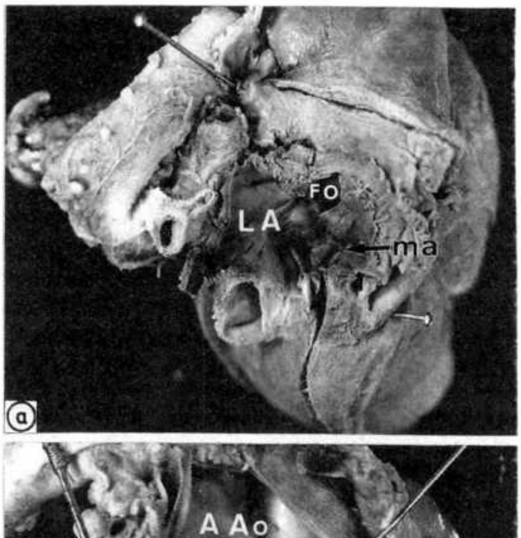

Figure 2 (a) A small left atrium with mitral valve atresia. The pulmonary veins were correctly connected. The foramen ovale was patent. FO, foramen ovale. The black arrows + ma indicate the atretic mitral valve. (b) Absence of the aortic valve cusps with a normal sized left ventricle and intact ventricular septum. Both coronary arteries were present. Ab + black arrows indicate the absence of aortic valve cusps. A Ao, ascending aorta.

the cusp level. If the interventricular septum is intact the left ventricle is hypoplastic because it is not filled by blood from the right side or from the aortic root. The size of the left ventricle, however, is normal when there is regurgitation of the aortic valve. This regurgitation can be caused by a malfunctioning of the aortic valve cusps or by their absence, as in our case. When the patient was examined by cross sectional echocardiography the aortic valve cusps were not found and no echoes were detected in the zone of the valve ring. The coronary ostia were correctly situated in the left and right sinuses.

In cases of mitral atresia in which no septal defect is shown and the left ventricular cavity is well developed, aortic regurgitation should be suspected and can be confirmed by either continuous flow Doppler or saline contrast echocardiography after injection into the aortic root.

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NOTICES

British Cardiac Society

The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts was 19 January 1990.

Pulsed lasers in angioplasty

An international workshop on Pulsed Lasers in Angioplasty will be held under the auspices of the European Society of Cardiology working group of coronary flow and angina pectoris in Tübingen on 11 and 12 May 1990. Further information from Dr K R Karsch, Department of Cardiology, Medical Clinic, University of Tübingen, Otfried-Müller-Strasse 10, D-7400 Tübingen, Federal Republic of Germany.

Biomechanics

The 7th meeting of the European Society of Biomechanics will take place in Aarhus on 8 to 11 July 1990. For further information contact Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, DK-8200 Aarhus N, Denmark; phone +45 8616 7500, extension 4649; fax +45 8610 7733.

MEASUREMENT

Limitations of Doppler ultrasound in the assessment of the function of prosthetic mitral valves

John Chambers, Graham Jackson, David Jewitt

Abstract

Pressure half time has been assumed to be a relatively flow-independent measure of orifice area, but it may also be influenced by atrial and ventricular factors. Pressure half time and peak left ventricular inflow velocity were measured by continuous wave Doppler ultrasound in 164 patients with normally functioning Carpentier-Edwards, Björk-Shiley, and Starr-Edwards mitral prostheses. Pressure half time was shorter in the Bjork-Shiley than in the other valve types and peak transmitral velocity was highest in the Starr-Edwards prostheses. These differences, however, were partly explained by coexistent differences in transmitral flow. Filling time accounted for 19% and stroke volume for 15% of the variance in pressure half time compared with only 5·6% for prosthetic design and 0·4% for annulus diameter when each of these variables was considered alone. The design of the prosthesis explained 18% of the variance in peak transmitral velocity, while cardiac output and annulus diameter did not contribute significantly. With Doppler ultrasound it is impossible to define reliable normal ranges for prosthetic function independently of atrial and ventricular function. Formulas for orifice area based on peak transmitral velocity and flow seem more likely to reflect the behaviour of normally functioning prostheses than those based on pressure half time.

There are numerous published reports of mean values for pressure half time and peak transmitral velocity (or derived gradient and orifice area) in normally functioning mitral prostheses[1-11] (table 1). The implicit assumption has been that dysfunction can be detected as a departure from these values, but this has not been established and important, unexplained inconsistencies remain.

Pressure half time is assumed to be a reliable indicator of orifice area but it rarely correlates inversely with annulus diameter and may be surprisingly similar in prostheses of widely different design.[5 6 10] Furthermore, the mean pressure half time for one valve type can be highly variable[1 3 7] and is far longer for a tricuspid prosthesis than for a mitral prosthesis of the same diameter.[1] Evidence is growing that factors other than the behaviour of the prosthesis may affect pressure half time; these include the shape and time course of left ventricular filling, stroke volume, and the transmitral pressure difference at the start of diastole.[12-15] Except for

Table 1 Published values for pressure half time and effective orifice area (mean (SD))

Study	*Porcine bioprosthesis*	*Bjork-Shiley*	*Starr-Edwards*
Effective orifice area (Hatle formula)			
Williams and Labowitz[10]	2·1 (0·7)^{H,C} (n=16)	2·5 (0·8) (n=36)	2·0 (0·3) (n=10)
Panidis *et al*[5]	2·2 (0·7)^{H,C} (n=6)	2·2 (0·7) (n=8)	2·1 (0·5) (n=3)
Sagar *et al*[9]	1·3–1·9^{H} (n=23)	2·1–2·2 (n=17)	
Fawzy *et al*[4]	1·5 (0·3)^{C} (n=14)		
Alam *et al*[8]	2·0 (0·5)^{C} (n=105)		
Cooper *et al*[11]	2·6 (0·7)^{C} (n=25)		
Pressure half time			
Ryan *et al*[3]	136 (18)^{C} (n=29)		
Hatle and Angelsen[7]	135 (25)^{C} (n=13)		
Gibbs *et al*[12]	90 (23)^{C} (n=38)	77 (18) (n=31)	127 (24) (n=5)
Present study	105 (35)^{C} (n=78)	90 (30) (n=56)	115 (45) (n=30)

C, Carpentier-Edwards, H, Hancock.

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early work by Holen *et al*,[16] no study of prosthetic function by Doppler ultrasound has reported flow information.

The aim of this study was to compare the contribution of valve type or annulus diameter and blood flow to pressure half time and peak transmitral velocity in three different types of mitral prosthesis—a porcine bioprosthesis (Carpentier-Edwards) and tilting disc (Björk-Shiley) and caged ball (Starr-Edwards) mechanical prostheses.

Patients and methods

PATIENTS

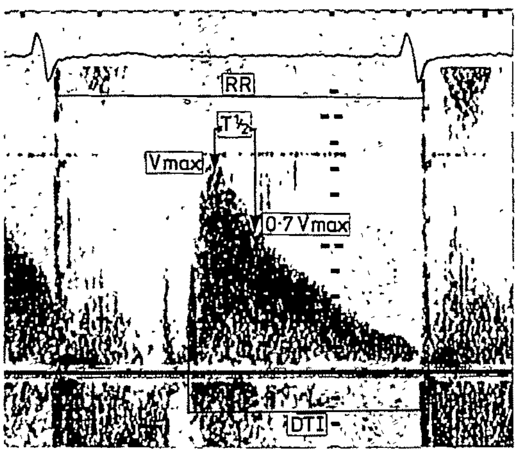
A total of 182 consecutive patients with Carpentier-Edwards, Bjork-Shiley, or Starr-Edwards prostheses were referred either for routine assessment or because dysfunction was suspected. Fourteen prostheses were excluded: 10 because of appreciable aortic or mitral regurgitation on continuous wave Doppler and colour flow mapping (area of jet (by planimetry) more than 20% of receiving chamber area)[17] and four because cusp thickness exceeded 3 mm.[18] No patient had reduced occluder motion. Four further patients were excluded because recordings were of poor quality. Abnormal left ventricular function was not a criterion for exclusion. Thirty five patients were in sinus rhythm, three were in paced rhythm, and the rest were in atrial fibrillation.

DOPPLER STUDIES

A phased array system was used (Hewlett Packard 77020A) with 1·9 MHz continuous wave and 2·5 MHz duplex probes. A full examination was performed in all views with sector imaging and colour flow Doppler to look for abnormalities of cusp or occluder motion and for significant aortic or mitral regurgitation. M mode recordings were taken at standard levels. A continuous wave probe was then placed at the apex, aimed towards the mitral valve, and its position adjusted until optimal signal quality was obtained. Left ventricular inflow recordings were made on to thermal paper run at 100 mm/s.

STATISTICAL ANALYSIS

All diastolic measurements were made on the same three cycles in each patient. Most waveforms had a non-linear deceleration phase. Pressure half time[19] was therefore calculated first by constructing a vertical line passing through the point of maximum velocity. A second line was then drawn parallel to the baseline at 0·7 × peak velocity. Pressure half time was taken as the distance along the second line from the first vertical line to the outline of the waveform (figure). The diastolic time interval was measured from the start of the mitral opening artefact to the midpoint of the closing artefact. On long cardiac cycles where ventricular filling ended before the end of diastole, the filling period was taken to end where transmitral velocity had fallen to less than 0·2 m/s for more than 200 ms. The filling period was shorter than the diastolic time interval in 34 (7%) of 492 cardiac cycles in a total of 19 patients. In all other instances the two periods were of identical length. The RR interval was measured from the end of the preceding diastolic period (figure). Mean values for pressure half time, peak transmitral velocity, diastolic time interval, filling period, and RR interval were calculated.



Left ventricular inflow recorded by continuous wave Doppler DTI, diastolic time interval; T½, pressure half time; V max, peak left ventricular inflow velocity.

Stroke volume was calculated from M mode left ventricular recordings by the corrected cube formula described by Teicholz *et al*,[20] which is not applicable in the presence of left ventricular dyskinesis. The formula could not, therefore, be applied in four cases. Cardiac output was calculated by the equation:

$$CO = (SV \times \text{rate})/10^3 \qquad (1)$$

when CO is cardiac output (l/min), SV is mean stroke volume (ml), and rate is heart rate derived from the mean cycle length over three cycles. Transmitral flow was calculated on each cardiac cycle from the formula:

$$Q = 10^3 \times SVm/DFP \qquad (2)$$

when Q is flow (ml/s), SVm is mean stroke volume (ml), and DFP is diastolic filling period (ms).

We used the SPSS^x program on the University of London computer for statistical analysis. It was first performed using the three individual values for pressure half time and peak transmitral velocity, but this gave results similar to those with the mean values for each patient. This may have been because there was little beat to beat variation in RR interval (F = 0·97; p = 0·38 by one way analysis of variance). Mean values were therefore used for further analysis. The factors controlling pressure half time and peak transmitral velocity were then assessed by multiple regressions by entering variables from among the following: diastolic time interval, diastolic filling period, transmitral flow, valve type, annulus diameter, cardiac output, presence of aortic regurgitation. The results for diastolic time interval were skewed and required log transformation before being analysed. Dummy variables were constructed for prosthetic type and annulus diameter. A p value of 0·01 was taken as significant for the multivariate analysis.

Table 2 Results for all annulus diameters combined (mean (SD))

Variable	*Carpentier-Edwards (n = 78)*	*Bjork-Shiley (n = 56)*	*Starr-Edwards (n = 30)*	*F value*	*p value**
T½ (ms)	105 (35)	90 (30)	115 (45)	4 0	<0 05
V max (m/s)	1 5 (0 3)	1 5 (0 4)	1 8 (0 3)	19 1	<0 0001
RR (ms)	760 (150)	760 (175)	790 (145)	0 9	
DTI (ms)	365 (130)	395 (140)	440 (120)	2 4	
Fill (ms)	365 (130)	355 (80)	415 (115)	5 5	<0 01
Age of valve (mnth)	35 (38)	51 (43)	107 (90)	—	
Age at surgery (yr)	59 (13)	56 (8)	49 (10)	—	
	n = 77	*n = 53*	*n = 30*		
SV (ml)	60 (25)	55 (20)	68 (20)	2 2	
CO (l/min)	4 8 (1 8)	4 6 (1 7)	4 9 (1 9)	2 6	
Flow (ml/s)	170 (60)	165 (55)	165 (80)	2 1	

T½, pressure half time, RR, RR interval, V max, peak left ventricular inflow velocity, DTI, diastolic time interval, Fill, diastolic filling period; SV, stroke volume, CO, cardiac output
*By one way analysis of variance

Table 3 Results for Carpentier-Edwards prostheses by diameter (mean (SD))

Variable	*27 mm (n = 2)*	*29 mm (n = 30)*	*31 mm (n = 27)*	*33 mm (n = 19)*	*F values*	*p value**
T½ (ms)	90 (10)	115 (35)	105 (40)	95 (30)	1 2	
V max (m/s)	1 7 (0 7)	1 5 (0 3)	1 5 (0 3)	1 4 (0 2)	0 8	
RR (ms)	645 (135)	830 (155)	755 (150)	680 (100)	4 9	<0 001
DTI (ms)	270 (85)	435 (130)	365 (115)	335 (70)	4 1	<0 001
Fill (ms)	270 (85)	405 (105)	355 (100)	330 (70)	4 2	<0 001
	n = 2	*n = 30*	*n = 27*	*n = 18*		
SV (ml)	45 (15)	60 (20)	60 (30)	60 (20)	0 2	
CO (l/min)	4 3 (2 3)	4 3 (1 6)	4 9 (2·1)	5 4 (1 5)	2 2	
Flow (ml/s)	180 (110)	145 (50)	180 (70)	185 (45)	2 9	<0 05

See footnote to table 2 for abbreviations
*By one way analysis of variance.

Results

MEAN PRESSURE HALF TIME AND PEAK TRANSMITRAL VELOCITY

These are shown for each valve type (table 2) and by annulus diameter within each valve type (tables 3–5). Pressure half time was shorter in the Bjork-Shiley prosthesis than in either of the other valve types ($p < 0\ 05$) and peak transmitral velocity was highest in the Starr-Edwards prostheses ($p < 0{\cdot}0001$). The relative contribution of prosthesis related and other factors was, however, unclear from this preliminary analysis because there were coexistent differences in cardiac output and filling period between different valve types and annulus diameters. Further multivariate analysis was therefore performed to try to dissociate these factors.

MULTIVARIATE ANALYSIS OF PRESSURE HALF TIME

Filling time and stroke volume were the variables that best explained the variance in mean pressure half time (table 6). Valve design also contributed, but annulus diameter, transmitral flow, or the presence of mild aortic regurgitation did not. All the contributory variables together explained 32% of the variance in pressure half time.

Even when each valve type was considered separately, annulus diameter did not explain a significant proportion of the variance in pressure half time (Carpentier-Edwards 4·9%, $F_{3,72} = 1{\cdot}2$; Björk-Shiley 4·5%, $F_{3,51} = 0\ 8$; Starr-Edwards 7 7%, $F_{2,25} = 1{\cdot}1$). The effect of filling time was greater in the Bjork-Shiley prostheses (24%, $F_{1,53} = 16{\cdot}7$; $p = 0{\cdot}0001$) than in the Starr-Edwards (20%, $F_{1,26} = 6{\cdot}7$; $p = 0{\cdot}016$), or Carpentier-Edwards prostheses (13%, $F_{1,74} = 10{\cdot}6$; $p = 0{\cdot}0017$).

To exclude the possibility that filling period was controlled by valve type or annulus diameter and that pressure half time could therefore be related indirectly to prosthetic factors, further analysis of filling period was performed. The filling period was strongly related to the RR interval (68%, $F_{1,162} = 343$; $p < 0{\cdot}00001$) in all three prosthetic designs and multivariate analysis showed little contribution from valve design alone (5·0%, $F_{2,161} = 4{\cdot}2$; $p = 0{\cdot}016$) or annulus diameter alone (4·0%, $F_{3,160} = 2\ 2$; $p = 0{\cdot}09$).

Table 4 Results for Bjork-Shiley prostheses by diameter (mean (SD))

Variable	*25 mm (n = 1)*	*27 mm (n = 18)*	*29 mm (n = 19)*	*31 mm (n = 13)*	*33 mm (n = 5)*	*F values*
T½ (ms)	100	100 (35)	90 (25)	90 (25)	75 (25)	0 7
V max (m/s)	1 9	1 6 (0 3)	1 4 (0 4)	1 6 (0 3)	1 3 (0 6)	1 4
RR (ms)	1065	755 (180)	760 (185)	760 (170)	710 (165)	0 8
DTI (ms)	615	405 (130)	395 (155)	390 (130)	340 (105)	0 9
Fill (ms)	485	360 (70)	350 (85)	360 (80)	315 (70)	1 1
	n = 1	*n = 18*	*n = 16*	*n = 13*	*n = 5*	
SV (ml)	60	50 (20)	60 (25)	65 (20)	45 (10)	1 4
CO (l/min)	3 4	4 2 (1 9)	5 0 (1 6)	5 0 (1 5)	4 0 (1 5)	0 7
Flow (ml/s)	125	145 (60)	175 (45)	180 (50)	150 (55)	1 2

See footnote to table 2 for abbreviations

Table 5 *Results for Starr-Edwards prostheses by diameter (mean (SD))*

Variable	*28 mm (n=7)*	*30 mm (n=14)*	*32 mm (n=9)*	*F values*	*p value**
T½ (ms)	130 (25)	100 (40)	125 (60)	1·1	
V max (m/s)	1·8 (0·2)	1·8 (0·2)	1·9 (0·4)	0·3	
RR (ms)	840 (85)	740 (170)	775 (190)	0·5	
DTI (ms)	460 (75)	445 (125)	415 (150)	0·3	
Fill (ms)	440 (50)	415 (135)	395 (130)	0·3	
	n=7	*n=14*	*n=9*		
SV (ml)	70 (10)	50 (15)	70 (20)	6·9	<0·01
CO (l/min)	5·2 (0·9)	4·1 (1·7)	5·9 (2·4)	5·4	<0·02
Flow (ml/s)	165 (35)	135 (65)	210 (105)	2·4	

See footnote to table 2 for abbreviations
*By one way analysis of variance

Table 6 *Results of multivariate regression analyses of the variance in pressure half time*

Variable	*Variance explained*	*F value*	*p value*	*Standard error*
Diastolic filling time	19%	37	<0·00001	33
Stroke volume	15%	26	<0·00001	35
Diastolic time interval	11%	19	<0·00001	35
Prosthetic design	5·6%	4·6	<0·02	36
Mean transmitral flow	2·0%	2·0	0·12	38
Coexistent aortic prosthesis	0·7%	1·3	0·25	37
Annulus diameter	0·4%	0·2	0·95	37
Presence of aortic regurgitation	0·0	0·0	0·85	37

MULTIVARIATE ANALYSIS OF PEAK TRANSMITRAL VELOCITY

Prosthetic design, cardiac output, and annulus diameter together explained 22% of the variance in peak transmitral velocity, of which most was explained by design alone (18%, ($F_{2,161}$ = 17·2; $p < 0·00001$)). Cardiac output explained only 2·7%, ($F_{1,158}$ = 4·3) and annulus diameter alone was not a determinant of peak transmitral velocity even within each prosthetic design (Carpentier-Edwards 3·5%, $F_{3,74}$ = 0·8; Björk-Shiley 6·0%, $F_{3,52}$ = 1·1; Starr-Edwards 2·0%, $F_{2,27}$ = 0·3). The prosthetic designs differed in their response to flow. Peak transmitral velocity was weakly but significantly correlated with cardiac output (r = 0·443; SE 0·24; $p < 0·02$).

Discussion

In the normally functioning mitral prostheses in this study, the variability in pressure half time was better explained by the diastolic filling period and stroke volume than by the design of the prosthesis. Annulus diameter did not contribute significantly.

DETERMINANTS OF PRESSURE HALF TIME

Theoretical work suggests that pressure half time is related not only to mitral orifice area, but also to the transmitral pressure difference at the start of diastole, to stroke volume, and to left atrial and ventricular compliance.[14 15] In a flow simulator we showed that the pressure half time in mitral bioprostheses reflects the shape and time course of the left ventricular filling curve[12] and this can be regarded as a model for the effect of left atrial and ventricular compliance. Altered atrial compliance may also explain the deterioration soon after balloon dilatation in the correlation between pressure half time and the orifice area measured by planimetry in patients with native mitral stenosis.[21]

The present study gives clinical evidence for a relation between pressure half time and both stroke volume and heart rate. All variables together, however, explained only 32% of the variance in pressure half time. Differences in ventricular compliance probably accounted for part of the residual variability, although inaccuracies in measurement or individual patient variability may also have contributed.

EFFECT OF HEART RATE ON PRESSURE HALF TIME

Morrow *et al* showed that in native mitral valves the proportion of left atrial pressure lost in the first 100 ms of diastole was high in pure mitral regurgitation, low in pure mitral stenosis, and intermediate in normal valves or in valves with combined stenosis and regurgitation.[22] This observation led to the concept of pressure half time, which was the time taken for the peak transmitral pressure gradient at cardiac catheterisation to fall to one half.[23 24] This was thought to be relatively independent of flow, but the original data show a large scatter in results with pressure half times of from 110 to 170 ms over a range of instantaneous heart rates from 63 to 86 beats/minute in atrial fibrillation.[24] Retrospective analysis of these data showed a statistically significant inverse relation between pressure half time and heart rate.[14]

An inverse relation between pressure half time and heart rate was also found during pacing in patients with permanent pacemaker systems and mitral prostheses.[13] Heart rate probably affects pressure half time in several ways. Orifice area may sometimes increase at higher heart rates, although at the cardiac outputs seen in the present study most valves would be expected to have been fully open.[25] Furthermore, pressure half time also falls as rate increases in patients with St Jude bi-leaflet tilting disc prostheses, which are expected to be fully open at low flows.[26] Changes in heart rate may also affect left ventricular compliance, stroke volume, and left atrial pressure.[27-29] The effect of these factors may differ in individuals because in the present study the observed relation between heart rate and pressure half time varied widely. Therefore no simple correction of pressure half time for rate can be possible.

EFFECT OF ANNULUS DIAMETER AND TYPE OF PROSTHESIS

The inability of this study to show a major effect of prosthetic design and annulus diameter on pressure half time need not necessarily rule out an effect of orifice area. In the Carpentier-Edwards porcine bioprosthesis actual orifice area may vary by about 20% in valves of the same annulus diameter[30] and in the Starr-Edwards valve there is no simple central orifice. The Björk-Shiley tilting disc prosthesis, however, has an area available for flow that is expected to reflect the annulus diameter more closely, but even in this valve type pressure half time was not related statistically to annulus diameter. It is possible that the type of prosthesis might have contributed more to the variance in pressure half time had valves with larger orifice areas such as the St Jude prosthesis been studied.[31] If, however, valve behaviour were a major determinant of pressure half time, this should have been found in the prostheses studied because these show wide differences during in vitro testing.[32 33] Furthermore, we found that pressure half time is only moderately related to orifice area in vitro.[12] Thus there is good evidence that in normally functioning mitral prostheses pressure half time does not reliably reflect orifice area.

PEAK TRANSMITRAL VELOCITY

Peak transmitral velocity was most closely related to prosthetic design although in the Starr-Edwards prostheses it was also affected by cardiac output. This result is consistent with hydrodynamic work, showing that of the three valve types studied the Starr-Edwards offers the greatest resistance to flow and therefore produces the steepest slope when transmitral velocity is plotted against flow.[32 33] A close relation between flow and peak velocity has also been shown in fixed diaphragm obstructions.[34]

CLINICAL IMPORTANCE

The relatively minor effect of prosthetic design on pressure half time has important practical implications. Numerous studies have attempted to define normal ranges for prosthetic function based on pressure half time or effective orifice area derived from the Hatle formula (220/pressure half time) (table 1). Differences between studies are likely to be related more to atrial or ventricular factors than to prosthetic function. Thus the range in mean pressure half time reported as normal for Carpentier-Edwards prostheses, 90–136 ms, is wider than for the three prosthetic designs in this study.

It is therefore very unlikely that pressure half time can reliably detect minor changes in prosthetic function. Studies claiming that Doppler is highly sensitive for the detection of prosthetic obstruction have used patients already defined as normal or dysfunctional on clinical grounds.[3 4 8 9] None the less, severe prosthetic obstruction is associated with a lengthened pressure half time.[3] Furthermore, aortic regurgitation has been reported to lengthen pressure half time when the mitral valve is normal, but to have no effect where there is severe mitral stenosis.[35 36] These observations are consistent with the suggestion that orifice area is the most important constraint on pressure half time where there is significant mitral stenosis, whereas where the orifice is relatively large, other factors will be more important. The point at which this transition occurs is not yet known.

This study showed that pressure half time was statistically more closely related to diastolic filling time and stroke volume than to prosthetic design or annulus diameter. Peak transmitral velocity was related to prosthetic design and in the Starr-Edwards valve also to cardiac output. Pressure half time is unlikely to detect small changes in orifice area. Orifice area formulas based on transmitral velocity and flow such as the Gorlin formula[25] are likely to reflect prosthetic mitral behaviour more accurately than the Hatle formula, which should be applied with caution in normally functioning mitral valve prostheses.

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MEASUREMENT

Automated non-invasive measurement of cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution and thermodilution

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Abstract

The accuracy and reproducibility of indirect measurement of cardiac output at rest by the carbon dioxide rebreathing (indirect Fick) method with an automated respiratory analysis system (Gould 9000IV) were compared with simultaneous measurements made in duplicate by dye dilution and thermodilution in 25 patients having cardiac catheterisation studies. Measurements of cardiac output by the carbon dioxide rebreathing method were not significantly different from those obtained with dye dilution (mean difference −0·3 l/min, SD 0·76, 95% confidence interval −0·7 to 0·1). Thermodilution significantly overestimated cardiac output by a mean of 2·2 l/min or 39% (SD 1·5, 95% confidence interval 1·6 to 2·8) compared with the carbon dioxide rebreathing method and significantly overestimated cardiac output by 1·9 l/min or 31% (SD 1·2, 95% confidence interval 1·2 to 2·5) compared with dye dilution. The reproducibility of measurements of cardiac output in individual patients was satisfactory with the dye dilution method but was poor with carbon dioxide rebreathing and thermodilution.

Indirect measurement of resting cardiac output by the Gould 9000IV automated carbon dioxide rebreathing method is more accurate but the variability inherent with this method requires that multiple measurements be taken for each determination. Measurement of cardiac output by the thermodilution method by a commercially available cardiac output computer was not satisfactory because not only was there considerable variability between repeat measurements but the method also consistently overestimated cardiac output compared with the dye dilution method.

Although cardiac output is a haemodynamic variable of considerable interest in clinical cardiology and cardiovascular research, simple and accurate non-invasive methods for its measurement have not been readily available. In current practice the indicator dilution methods, dye dilution and thermodilution, have replaced the direct Fick method because of their relative ease and suitability for automation.[1,2] The invasive nature of these techniques limits their application and accordingly non-invasive methods including electrical bioimpedance cardiography,[3] echocardiography,[4,5] radionuclide angiography,[6] and the indirect Fick method[7] have been developed. These methods can be used for serial estimations but are limited by technical difficulty or doubts about their accuracy.[8,9]

The indirect Fick or carbon dioxide rebreathing method has been available for many years and in general has an accuracy for measurement of cardiac output similar to that of other methods.[10-12] The Gould 9000IV cardiopulmonary exercise system (Gould, Dayton, Ohio) is an automated system for respiratory analysis that has removed much of the technical difficulty in performing indirect Fick measurements. It is relatively easy to use and is ideal for performing repeated estimates of cardiac output in ambulatory individuals.[13]

We compared indirect Fick measurements of cardiac output made by the Gould 9000IV with simultaneous measurements of cardiac output made by dye dilution and thermodilution and we obtained a measure of the reproducibility of each method. Previous studies have largely relied upon correlation to compare methods.[10,11,14] While two estimates may be highly correlated the estimates may still show poor agreement in individual subjects.[15,16] We used the method of Bland and Altman[15] to examine the agreement between and the reproducibility of different methods for estimating cardiac output.

Patients and methods

PATIENTS

We studied 25 patients undergoing diagnostic right and left heart catheterisation for valvar heart disease or cardiomyopathy. There were 17 men and eight women (aged 28–80 years (median = 67). In all but one a multiple lumen thermistor tipped catheter (Swan-Ganz) was placed into the pulmonary artery via the right femoral vein. The left heart catheter was inserted via the right femoral artery. All patients were fully informed of the study details and then gave written consent to participation. The study was approved by the committee on clinical investigation of the Flinders Medical Centre.

CARBON DIOXIDE REBREATHING MEASUREMENTS (INDIRECT FICK)

The Gould 9000IV consists of an infrared absorption analyser for carbon dioxide, a paramagnetic oxygen analyser, a dry rolling seal spirometer, and a microcomputer with an analogue to digital converter and a printer. It provides measurements of the concentration of expired carbon dioxide with resolution to 0·01% and an accuracy of ±0·1% when measuring concentrations from 0 to 10%. Minute volume is measured with resolution to 0·01 l/min and an accuracy of ±0·025 l/min. These variables have been independently validated.[17] The analysers and the spirometer were calibrated before each study according to the manufacturer's instructions.

With this method the cardiac output is calculated by the equation:

$$\text{Cardiac output} = V\text{co}_2/(C\text{vco}_2 - C\text{aco}_2)$$

where $V\text{co}_2$ is the rate of production of carbon dioxide per minute calculated from continuous measurements of expired minute volume and the concentration of carbon dioxide in expired gas. $C\text{vco}_2$ is the concentration of carbon dioxide in mixed venous blood and $C\text{aco}_2$ is the concentration of carbon dioxide in arterial blood. The arteriovenous difference in the concentration of carbon dioxide is calculated by the formula:

$$C\text{vco}_2 - C\text{aco}_2 = 11{\cdot}02(P\text{vco}_2^{\,0\cdot396} - P\text{aco}_2^{\,0\cdot396})$$

where $P\text{vco}_2$ and $P\text{aco}_2$ are the partial pressure of carbon dioxide in venous and arterial blood respectively.[18-20] A haemoglobin concentration of 150 g/l and oxygen saturation of 95% was assumed. The partial pressure of carbon dioxide in arterial blood was estimated from the concentration of carbon dioxide in expired gas at the end of expiration. The carbon dioxide tension of mixed venous blood was estimated in a similar way by using the equilibrium rebreathing procedure described by Collier.[21] The individual respired from an anaesthetic bag filled with a mixture of approximately 10% carbon dioxide in oxygen. The volume in the bag was fixed at 1·5 times the mean tidal volume of the preceding respirations. During the rebreathing procedure the end tidal concentration of carbon dioxide was displayed on the computer screen so that the operator could signal to the computer that a satisfactory equilibrium had been achieved. The equilibrium value was used to estimate the mixed venous carbon dioxide tension. No correction was made for differences between blood and alveolar tensions.[10 18 22] The computer performed all the calculations and displayed the estimated cardiac output.

THERMODILUTION MEASUREMENTS

Measurements of cardiac output were taken using the 7 French pulmonary arterial catheter (Swan-Ganz, 93A-151-7F, American Edwards Laboratories, Anasco, Puerto Rico) linked to a 9520A cardiac output computer (Edwards Laboratories, Santa Ana, California). Ten ml of iced 5% dextrose drawn into a 10 ml plastic syringe was hand injected into the right atrium via the proximal lumen of the Swan-Ganz catheter. The thermodilution cardiac output was taken as the value for the second of two or three injections.

DYE DILUTION MEASUREMENTS

Dye dilution measurements were made with 5 or 10 mg of indocyanine green (Cardio-green, HW&D, Baltimore, Maryland) (the larger dose was used for those with mitral valve disease) injected by hand into the right atrium via the proximal lumen of the Swan-Ganz pulmonary artery catheter. Arterial blood was drawn from the proximal aorta through a DC-410 photoelectric detector with a SW-367 pump (Waters Instruments, Rochester, Minnesota). Cardiac output was calculated with a CO-10 cardiac output computer (Waters Instruments).

EXPERIMENTAL PROTOCOL

All measurements of cardiac output were taken at the end of the diagnostic study. The patients remained supine and breathed room air via a respiratory valve connected by a flexible hose to the spirometer of the Gould 9000IV so that all expired gas could be collected and analysed. Indocyanine green was injected at the onset of carbon dioxide rebreathing and this injection was immediately followed by the two or three injections of thermodilution indicator. This sequence was repeated within approximately 10 minutes. In the patients who were not given indocyanine green, the thermodilution indicator was injected at the start of the rebreathing procedure. From the 25 subjects we obtained 24 duplicate indirect Fick measurements with 24 paired thermodilution readings, and 19 pairs of measurements for dye dilution. This gave 23 comparisons between the carbon dioxide rebreathing and thermodilution methods and 18 comparisons between the indirect Fick and dye dilution methods and between thermodilution and dye dilution. In 17 of the patients cardiac output was estimated using all three methods.

ANALYSIS

For each patient the cardiac output by each of the three methods was taken as the mean of the two measurements with each method. The values of cardiac output in each subject obtained by the three methods were compared by analysis of variance in a repeated measures two factor design. Individual comparisons were made by the Newman-Keuls multiple range test. Differences between cardiac output values obtained by the three methods were examined by the method of Bland and Altman in which the individual differences between the two methods in each individual are plotted against the average value obtained from both methods in that individual.[15] The mean, standard deviation, and 95% confidence interval of the differences were calculated. We also compared mean values for each method with one

Table 1 Reproducibility of different methods for estimating cardiac output

Comparison (n)	*Dye₁/Dye₂ (19)*	*Fick₁/Fick₂ (24)*	*Thermal₁/Thermal₂ (24)*
Mean difference (l/min) between duplicates	0·22	−0·31	−0·39
Standard deviation of difference	0·44	1·35	1·11
Coefficient of repeatability (2 × SD)	0·88	2·7	2·2

another using scatter plots.

The accuracy of both the carbon dioxide rebreathing and thermodilution methods was assessed from the mean differences between each of these methods and dye dilution. The "limits of agreement"[15] were calculated from the mean difference plus and minus twice the standard deviation of the difference such that 95% of differences were within that range. The differences between the values obtained in each individual for the carbon dioxide rebreathing and thermodilution methods were examined in a similar fashion.

The reproducibility (repeatability) of each method was examined by plotting the differences between duplicate measurements against the average of the two measurements.[15] The mean and standard deviation of the differences between the two readings were calculated so that the "coefficient of repeatability"[15] (twice the standard deviation of the differences) could be calculated.

Results

REPRODUCIBILITY OF DIFFERENT METHODS FOR CARDIAC OUTPUT

For each method there was no significant difference between the duplicate measurements (table 1). For dye dilution all of the differences were less than 16% of the mean value (fig 1a). For the indirect Fick method the reproducibility was low with only 50% of the differences being within 20% of the mean value (fig 1c). For thermodilution reproducibility was such that 70% of the differences were within 20% of the mean value (fig 1b).

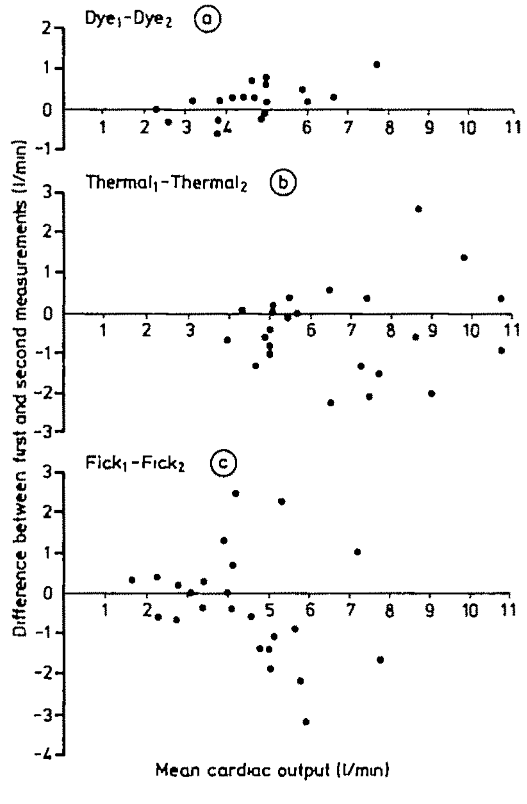

Figure 1 Differences between the first and second estimate of cardiac output with each method plotted against the mean of those two measurements by dye dilution (a), thermodilution (b), and indirect Fick (c)

DIFFERENCES BETWEEN METHODS

The mean values with the indirect Fick method and the dye dilution method were not significantly different, although the limits of agreement were wide (table 2) with 28% of the differences being $>20\%$ of the mean value (fig 2a). The mean thermodilution value was 31% greater than the dye dilution value ($p < 0{\cdot}001$) and 39% greater than that by the indirect Fick method ($p < 0{\cdot}001$) (table 2). For both comparisons with thermodilution the range of differences was wide (fig 2).

Discussion

In this study we found no systematic difference between estimates of cardiac output made by the indirect Fick and dye dilution methods but measurements obtained by the thermodilution method consistently overestimated the cardiac output compared with measurements obtained by the other two methods. The reproducibility of estimates of cardiac output within an individual was significantly worse for mesurements obtained by carbon dioxide rebreathing or by thermodilution than it was for those obtained by dye dilution. The poor reproducibility of these two methods contributed to the wide range of differences seen between methods.

Several factors contribute to the considerable variation seen between repeated measurements of cardiac output with any one method. One important factor is that the cardiac output is not a tightly regulated haemodynamic variable such as blood pressure[23] and biological variability between measurements is considerable.[24 25] In addition, both thermodilution and dye dilution are subject to random errors owing to variation in the dose of indicator and its rate of injection, to the pulsatile nature of blood flow, and to variation in the calculation of the area under the indicator dilution curve.[1 24 26] Thermodilution is also subject to variation from the placement of the thermistor in the pulmonary artery and from physiological variations in the temperature of pulmonary arterial blood with respiration.[1 24 26] For indirect Fick measurements of cardiac output small random errors in the estimation of the arterial and mixed venous carbon dioxide concentrations from the end tidal and the rebreathing equilibrium concentrations of carbon dioxide can result in relatively large errors in the estimate of the arteriovenous difference for carbon dioxide concentration.[27 28] This problem seems to be less important when the arteriovenous difference is large such as during exercise, when the carbon dioxide rebreathing method has been found to be more reliable.[7 27 29] Another important source of variation is that small deviations in ventilation and alveolar carbon dioxide tension can result in large changes in carbon dioxide transfer and thus carbon dioxide production.[28]

Table 2 Comparisons of different methods for cardiac output

Comparison (n)	*Fick-Dye (18)*	*Thermal-Dye (18)*	*Thermal-Fick (23)*
Mean difference	−0 28	1 85*	2 16*
(l/min) (95% CI)	(−0 66 to 0 07)	(1 24 to 2 47)	(1 52 to 2 79)
Standard deviation of difference	0 76	1 24	1 49
Lower limit of agreement	−1 80	−0 63	−0 82
(95% CI)	(−2 45 to −1 15)	(−1 18 to −0 08)	(4 09 to 6·19)
Upper limit of agreement	1 24	4 33	5 14
(95% CI)	(0 59 to 1 89)	(3 78 to 4 87)	(−1 87 to 0 23)

*p < 0 001

Apparent differences between estimates of cardiac output by any two methods may stem both from random variation within each individual method (poor reproducibility) or from systematic differences between one method and another. The dye dilution method has been accepted as a "gold standard" because no systematic bias has been found between direct (oxygen) Fick and dye dilution estimates of cardiac output.[30,31] Our results for the comparison of indirect Fick and dye dilution estimates of cardiac output are consistent with such previous observations and with comparisons of the indirect Fick method with dye dilution[7,12] or with the direct Fick method.[11,24] The thermodilution method is well established in clinical practice and is capable of providing accurate estimates of cardiac output provided that appropriate corrections are made for several potential errors.[10,26] The method is subject to overestimation of cardiac output, such as that observed in this study, owing to loss of indicator before and after injection.[1,26] Loss of indicator can be reduced by injection at ambient temperature at the expense of a reduction in the thermistor signal to noise ratio and thus greater variability in the estimate of cardiac output.[1] The thermodilution cardiac output computer used in this study uses a computation constant to adjust for loss of indicator with different Swan-Ganz catheters that is derived from an "in vitro study" (product literature). The recommended constant may not be correct for catheters inserted from the femoral vein where the longer intravascular course could result in greater loss of indicator. None the less, an in vitro study using thermodilution cardiac output computers (including the model used in this study) obtained similar overestimates of cardiac output under conditions of cold injection and pulsatile flow.[1] The computer used in the present study also overestimated cardiac output when compared with invasive Fick measurements in another study.[32] Further evaluation of such devices is needed before they can be used as a standard for comparison with other methods.[1,33]

In previous studies comparing different methods for estimating cardiac output the range of differences between estimates has been wide and a considerable number of differences were >25% of the mean value.[7,12,22] The range of differences seen in the present study is similar to that reported between direct Fick and indirect Fick[11,22,29] or dye dilution[7,31] estimates. Such observations are consistent with the inherent variability of cardiac output and of the methods available for its estimation.

We found that indirect Fick estimates of resting cardiac output measured by the Gould 9000IV are accurate but that the variability of estimates is large. Averaging of repeated measurements is required to achieve a reliable estimate of cardiac output in individual subjects.

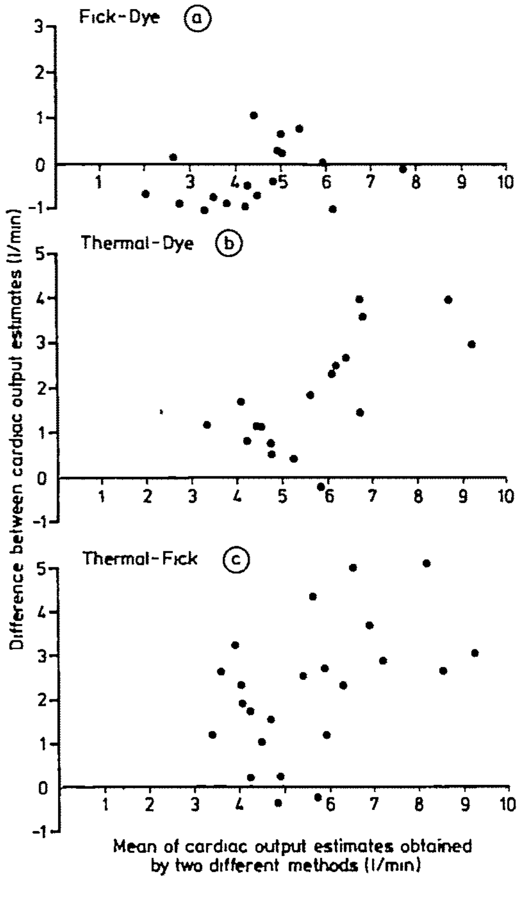

Figure 2 Differences between cardiac output estimates by two different methods plotted against the mean of those two estimates; indirect Fick and dye dilution (a); themodilution and dye dilution (b); indirect Fick and thermodilution (c).

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BRITISH CARDIOLOGY

Bernard A Robinson 1888–1979: an unknown pioneer of electrocardiography

A Hollman

The important contributions of Bernard A Robinson (1888–1979) (fig 1) to the early development of the electrocardiograph and of other scientific instruments have largely gone unnoticed. He is not mentioned in major British papers on the history of electrocardiography.[1-3] When I visited him in 1976 I was impressed to find that he had kept all his working notebooks, which were full of detail about the supply and testing of equipment. After his death these notebooks and his other papers were placed in the Science Museum Library, London.[4] They are catalogued in six sections: notebooks (ROB1), correspondence and historical material (ROB2), internal technical memoranda (ROB3), instrument instructions (ROB4), other technical material (ROB5), and printed papers and catalogues (ROB6). There is a good deal of useful material in this collection not only about the early years of electrocardiography but also about other electrical instruments such as the Bock-Thoma heat recorder. This paper is based on our conversation and on an account he gave me of his work with Thomas Lewis.[5]

Visit to Einthoven

Robinson studied physics and electrical engineering in London and in 1905 he joined the Amalgamated Radio Telegraph Company at Cullercoats near Newcastle upon Tyne. Early in 1907 the company sent him to Professor Willem Einthoven's department in Leiden to obtain a model of the string galvanometer that Einthoven had invented in 1901.[6] With the use of this instrument the earliest high speed *radio*-telegraph messages were transmitted at 110 signals per minute from Newcastle to Copenhagen and he became the first person to hear speech sent across the North Sea. He recalled that there were several models, all neat and about 6 inches high, with gold or platinum strings. Einthoven generously gave original electrocardiograms to Robinson and also copies of his articles, one of which (ROB5/1) is notable because the 16 pages are handwritten by himself (fig 2) in excellent colloquial English despite being a translation of a German paper.[7] Professor H A Snellen kindly identified this reference and writes, "Einthoven certainly had a gift for languages. He learnt English, German and French at high school, and Latin and Greek afterwards. Later in life he was often heard to quote Latin authors. As you probably know he often published the same material two or three times in different languages with rather slight changes or even just translated literally. His teacher, Donders, often did the same, in contrast to Lewis." It is said that Einthoven perfected his English by reading a chapter of an English classic in bed every night.[2] It is certainly a tribute to the warmth of Einthoven's personality that he went to so much trouble for a young non-medical visitor.

Figure 1 B A Robinson circa 1925.

The Cambridge electrocardiograph

The Cambridge Scientific Instrument Company had a royalty agreement with Einthoven to manufacture his string galvanometer and W D Duddell, FRS, inventor

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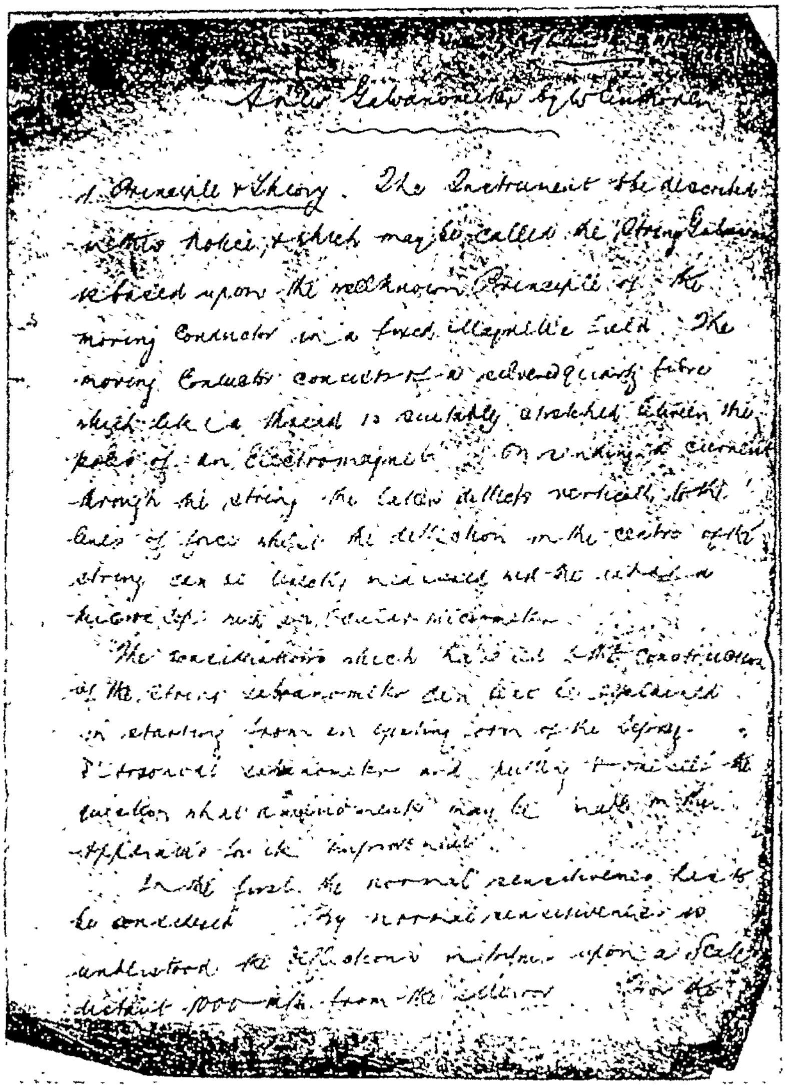


Figure 2 Page 1 of a 16 page manuscript with the annotation "Written by Prof Einthoven to B.A.R." It is a translation of the article "Ein neues galvanometer."[7] It reads . .

A new galvanometer by W Einthoven

Principle and Theory.

The Instrument to be described in this notice, and which may be called the String Galvanometer is based upon the well known Principle of the moving conductor in a fixed magnetic field. The moving conductor consists of a silvered quartz fibre which like a thread is suitably stretched in between the poles of an Electromagnet. On sending a current through the string the latter deflects vertically to the lines of force whilst the deflection in the centre of the string can be directly measured with the aid of a microscope with an ocular micrometer

The considerations which have led to the construction of the string Galvanometer can best be explained in starting from an existing form of the Deprez-d'Arsonval Galvanometer and putting to oneself the question what amendments may be made on the apparatus for its improvement.

In the first the normal sensitiveness has to be considered. By normal sensitiveness is understood the deflections in m/ms upon a scale distant 1000 m/m from the mirror. For the . . .

of the Duddell oscillograph, produced a superb new design for them. The first one, a galvanometer only, was supplied to the physiological laboratory of Professor MacDonald at Sheffield late in 1905[3] while the first electrocardiograph went to Professor E A Schafer in Edinburgh in 1908 for physiological work and another early one was supplied to the Gutta Percha Company for electrical research—a reminder that Einthoven's invention benefited non-medical disciplines too. But for clinical work an entire assembly with all the associated equipment was required and the first complete Cambridge electrocardiograph "outfit," as Robinson called it, was made in 1911 and sent to Dr (later Sir) Thomas Lewis. Robinson had been recruited by Mr Robert Whipple to take charge of this development and he started work at Cambridge early in 1912 as assistant to Mr (later Sir) Horace Darwin.[8]

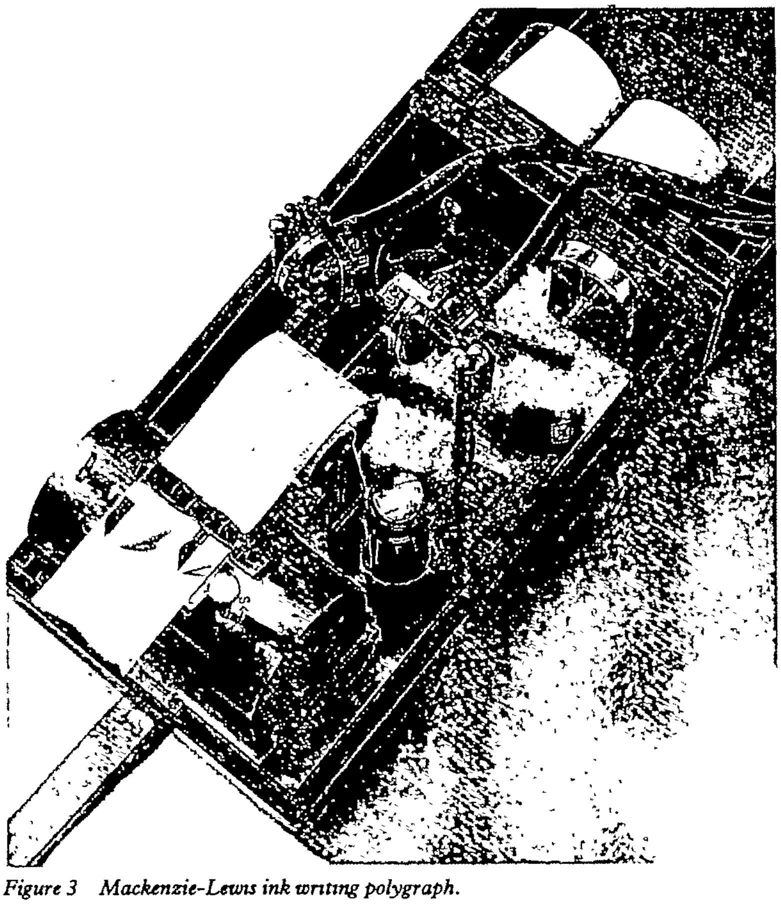
Working with Thomas Lewis

Robinson's work with Lewis is best told in his own words.[5]

> I was introduced to Dr. Lewis in July 1912. At that time he was working with an Edelmann String Galvanometer, and had not got the Cambridge instrument working. Thursday was his research day in each week and it was arranged that as much as possible I should spend Thursdays with him. This co-operation was the main factor in the very rapid development of the cardiograph between 1912 and 1915. It relieved Lewis of all responsibility for the operation of the instruments so that he could concentrate on the physiological side. At the same time I was on the spot to counter any difficulties and immediately report to Cambridge suggested modifications for regular hospital and clinical use. As each new type of equipment was produced it was submitted to him for criticism, and we used prototypes together before being put into production. From then onwards Lewis only used Cambridge equipment. Thus the Cardiograph became a unified Outfit and each one supplied strictly up-to-date.
>
> Lewis was 31 and I was 24 when I started working with him and that was an education in itself. During the three years I was associated with him so closely I never once saw him ruffled. He had a most equable temperament. Slim in figure, those penetrating eyes under heavy eyelashes were very expressive. Always quietly speaking, when anything went wrong we would look at each other and instinctively felt "Come on let's try again" He had infinite patience and there was much affection between us. He once told some visitors, "When 'BAR' is here the instruments always behave; so when he is away his photo hangs up".
>
> Most of the work at that time was done on anaesthetised dogs and Lewis was most careful that they were tenderly treated before being "put under"; and, never under any circumstances allowed to recover consciousness.
>
> One always had to have a plentiful supply of experimental electrodes ready. Prepared from approximately 3 mm od glass tubing and drawn out to about 1/2 mm bore, they were plugged with cotton wool saturated with 10% saline into which was embedded the thin connecting wire. Often half a dozen or more electrodes were in use at one time and the greatest care had to be taken in the positioning, and the right connection maintained for the recording. There was obvious pleasure in producing some irregular function of the heart; of taking the record, and then restoring normal rhythm without altering the position of electrodes. When we met a week later sometimes he would say "I'm puzzled by such and such a record last week so we must repeat and check each step." It really was a joy to work with him.

One of the major difficulties encountered by the Instrument Company in 1912 was the production of the "strings" for the galvanometers Einthoven used quartz and then electrically bombarded from a silver electrode to obtain the conducting surface. This was a slow process especially when the finished strings were required to be 150 mm long and 3 μ diameter. The most urgent task therefore at that time was to produce strings! Compared with quartz, soda-lime glass was not only much easier to draw but also took the silver plating better using the silver nitrate-Rochelle Salt formula. They were equally satisfactory in the galvanometers. Much work was done trying pure metals and other materials but finally silvered glass strings were standardised. The glass was drawn down to 1–1/2 to 2 μ, then silvered with 1/2 μ coating and finally burnished before mounting. The burnishing was necessary to consolidate the spongy coating and give a clean cut edge for photography. At a later date I concluded that maximum sensitivity was not required but rather minimum time period for cardiograph work. I cut the length of the strings down to 100 mm and resistance of about 3000 ohms. Lewis made a number of tests and agreed, so they became standard for all outfits from 1913 onwards. This also had the advantage of speeding up production. From 1912 to 1919 all strings were made, mounted, and tested by myself. To a large extent this was due to War conditions and the difficulty of obtaining sufficient skilled personnel.

Before 1920 it was my prerogative to see every Outfit in Great Britain properly installed and the Heart Specialist tutored in its operation. This led to many friendships with the Giants of those days such as Prof. A D Waller; Sir James Mackenzie; John Parkinson; John Cowan of Glasgow; Hay of Liverpool; Ritchie of Edinburgh; Wardrop Griffiths of Leeds; Professor Ernest Rutherford when at Manchester and at the Cavendish; and a host of others.



Science Museum London

Figure 3 Mackenzie-Lewis ink writing polygraph.

In the early days when dealing with human patients Lewis sometimes would take simultaneous Mackenzie Polygraph and Einthoven records. Early in 1914 I suggested to Lewis that the pneumatic system of the Polygraph was not designed for maximum sensitivity. He immediately took me round to Mackenzie in Harley Street to discuss the matter. Mackenzie agreed with me and it was decided to redesign the instrument. The first new model was tested out by Lewis in July 1914 and fully approved. It was known as the Mackenzie-Lewis Polygraph in honour of these two great savants. However only five were made owing to the emergencies of the War requiring all instrument production for war purposes. Three of the five were believed to have been destroyed during the Second World War

In the early days as cardiograph outfits became an essential equipment for Specialists so the analysis of records obtained often involved considerable ingenuity. I frequently received records staing that the sender could not decipher them and stating that it was "a quite unusual case". They did not like to send them to Lewis as they did not like to show their ignorance! The two main causes were either they had inserted the plate with the emulsion side reversed in the carrier, or else the right arm, left arm leads reversed by thinking of their own limbs instead of their patient. They were happy days of pioneering but very time absorbing when one was working all hours, seven days a week, under War conditions.

Robinson's warm account of Lewis's personality contrasts with the experience of others who found him difficult to know, impatient, and short tempered. Possibly co-workers with something to offer were more readily accepted as Paul White discovered when he showed Lewis how to use the slide rule. But it does emphasise Pickering's comment that those who gained his friendship knew a warm hearted man.

Robinson's expertise

Robinson's association is not mentioned in any of Lewis's papers nor is he acknowledged as part author of Chaper 1 of *Clinical Electrocardiography* but without his technical expertise Lewis would probably not have readily accomplished the work on the excitatory process in the dog's heart which won him his FRS. The new design of the polygraph was done entirely by Robinson who supervised its construction at Cambridge. Luckily he had kept an unused model and this (fig 3) is now in the Wellcome Museum of the History of Medicine at the Science Museum in London. The use of hard glass instead of quartz for the galvanometer string is not well known and its introduction was due to the invention in 1913 by Dr Keith Lucas of an electric heater to draw out the glass.[2]

The photographic recording of the electrocardiogram with the Cambridge apparatus was usually done on a glass plate but, like the Edelmann company, they also supplied a camera with a long roll of photographic paper which was very useful for arrhythmia analysis. Robinson again showed his technical ingenuity by inventing an automatic developing process for the paper which he called "photo-tape." He wrote a useful paper with illustrations on electrocardiography in 1914.[9]

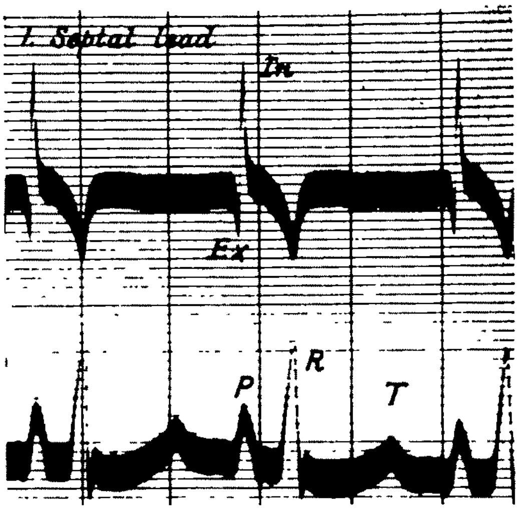


Figure 4 Twin channel electrocardiograms from a dog's heart. From the inter-atrial septum and lead II (lower trace). (Philos Trans R Soc Lond [Biol] 1914; 205: plate 40).

Mackenzie and Osler

Robinson had first met Sir James Mackenzie in Waller's laboratory in 1912 and in February 1913 visited him at 133 Harley Street and was taken out to dinner. Soon afterwards he installed a Cambridge electrocardiograph there and recalled that "I took a number of cases for him and met Sir William Osler, Dr. John Hay, Dr. Bertrand Dawson and Dr. William Price all seeing the new instrument and it was my privilege to teach all the above at a later date how to use the electrocardiograph." His notebook (ROB1/4) records that plate camera No 25147 was sent to Osler at Oxford on 16 October 1914 and this must have been a repair or replacement because Osler was supplied with an electrocardiograph on 1 January 1912.[3] But it was the 9th edition in 1920 of Osler's textbook edited after his death by T McCrae that first contained illustrations of electrocardiograms and they are not Cambridge recordings. Also in 1914 the Cambridge Company produced a double string carrier designed by W H Apthorpe that enabled two simultaneous recordings to be made with one galvanometer. Lewis used this extensively for his work on dogs (fig 4) and for phonocardiography (fig 5). One was sent to Einthoven in October 1914 but it seems doubtful if he ever used it. Professor Snellen writes, "As far as Einthoven's own galvanometer is concerned the ones he used were always made in his own laboratory with parts which he bought from specialised firms. When I worked in his laboratory three years after his death the room for electrocardiography was still intact but I saw only successive models of his own string galvanometer."

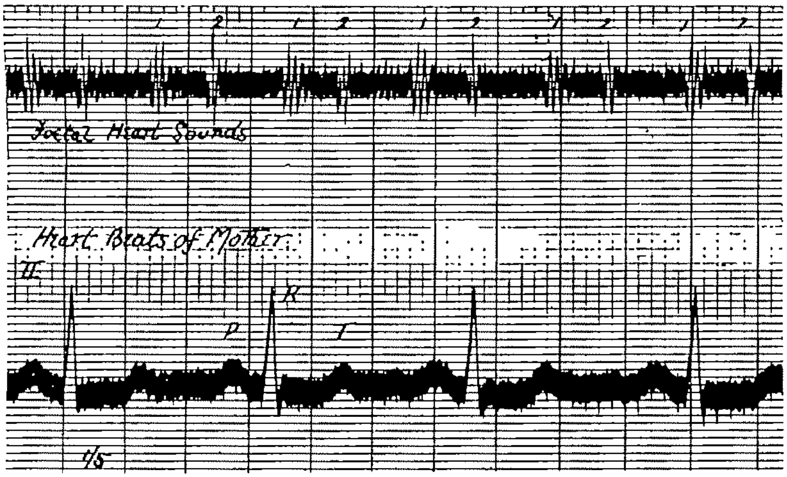


Figure 5 Simultaneous recording of the heart sounds of the fetus and the electrocardiogram of the mother made by Thomas Lewis in 1914. (Fig 5 in Barron SL[1]).

He was closely associated with Mackenzie too at the London Hospital whose outfit was installed in 1914. He recalled that "he was a very genial man that was the great thing about Mackenzie. I mean to say he would crack a joke about all sorts of things. He was a very charming man to talk to and work with." He admired "the marvellous John Parkinson" and related a remarkable incident involving him.

Factitious bradycardia at the London Hospital

For a demonstration Parkinson produced a healthy looking man of 26 and Robinson was dismayed to find a heart rate of about only 30 per minute. He thought something had gone wrong with the instrument but was immediately told that the patient was puzzling them and further that there were another nine apparently healthy young men with a similar rate. Electrocardiograms were taken from all of them and when repeated after 18 hours in hospital the heart rate was normal. Being unable to provide a medical explanation Parkinson asked Robinson to tackle the problem from the lay point of view. "After a time I got out of them that they were doping themselves. It was difficult to find out what was the dope because they did not wish to give it away but eventually they said it was the photographic chemicals metol and hydroquinone." They were simulating illness to avoid military service.

Robinson's papers in the Science Museum Library

By 1915 the Cambridge Scientific Instrument Company had made 35 complete electrocardiograph outfits and details of testing them are recorded in his two notebooks each of 254 pages (ROB1/3 and 1/4) that run from July 1912 to November 1918. These outfits went all over the world—for example, to Western Australia, Japan, Russia, India, France, and Canada, with 10 going to the USA. In addition, galvanometers only were sold, one of special construction being made for the Marconi Radio Telegraph Company. Other Cambridge equipment is also mentioned in the notebooks and includes the Duddell thermo-ammeter, a universal electrometer sent to Patna, an optical pyrometer, a thermo-couple potentiometer, and a sphygmo-oscillograph.

His correspondence (ROB2) is from 1952 to 1974. There are letters to the staff at Cambridge such as S L Barron and A F Wolfe and these contain valuable material on early electrocardiographic work and its pioneers. In one of them he tells of re-soldering a string for Sir William Hume "i.e. 45 years with the galvo!" Several letters between Dr George Burch and himself relate to the placement of historical artefacts in the Tulane University Museum. The internal technical memoranda (ROB3) contain material on the Bock-Thoma Universal Recorder. Instrument instructions (ROB4) include a description in 1913 of the use of electrodes made of sponges soaked in zinc sulphate and sodium chloride as a substitute for the current method of immersing the limbs in salt solution. The section labelled "other technical material" (ROB5) has a 32 page typescript from Einthoven (ROB5/2) entitled "Additional appreciations concerning the string galvanometer." The final section on "Printed papers and catalogues" (ROB6) is large and interesting. It contains three historical accounts of the Cambridge Company and five monographs, 12 catalogues, and seven construction booklets issued by them. There are also four long papers on the electrocardiogram by Dr M Edelmann, two papers by Robert S Whipple, and a signed reprint from Einthoven.

Later work in industry

During the first world war he was also closely involved with the design and production of instruments for gun ranging and at the end of the war he was appointed resident technical engineer for Cambridge at Newcastle upon Tyne. His work now was with industry and included equipment for locomotive testing and the automatic control of blast furnaces. He became a member of the Institution of Electrical Engineers and contributed two comprehensive papers to their journal. One dealt with the development of methods of measurement[10] and the other with electrical measuring instruments.[11] In the second world war he supervised the accuracy of Cambridge equipment used in ordnance and munition factories and after it he marked his retirement with an article that summarised 50 years of scientific instrument manufacture.[12]

Personal affairs

He and his wife, who had one son, were prominent in church affairs and they initiated a widely praised mission at Hexham, Northumberland, which they ran for 23 years. He was a diocesan reader for 58 years and was also a senior member of the British Red Cross Society.

I am indebted to Mr Alan Osborne for introducing me to Mr Robinson.

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Br Heart J 1990;63:205–6

BRITISH
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VIEWPOINT

Balloon dilatation of the aortic valve in adults: a surgeon's view

Tom Treasure

> There can be no more fascinating problem in surgery than the relief of pathological conditions of the valves of the heart.

Souttar wrote this to introduce his account of the first mitral commissurotomy, performed in The London Hospital in 1925. He pushed on the door that might have opened the way to valve surgery but it was kept securely shut.[1] Souttar still has his detractors—and true, there was more mitral regurgitation than would have been ideal both before and after this operation—but rather than listen to the oral tradition which seems to have grown up around this early attempt to open a stenotic valve, read his paper. He knew exactly what he was doing, as regards the surgical approach; the hazards of interfering with cerebral perfusion; and, in particular, what he was doing to the valve. Opinions on the "mechanism" of aortic balloon dilatation show much less insight.[2] And yet it was firmly believed for many years afterwards that relief of mitral stenosis would not help the patient. One of the sceptics, Sir Thomas Lewis (the "father of clinical science") wrote in 1943: "Although many symptoms may be complained of by the patients suffering from mitral stenosis, there are none that can be ascribed properly and usefully to this deformity of the valve",[3] an opinion proved wrong within a decade as closed valvotomy transformed the lives of thousands.

On the subject of aortic stenosis Lewis wrote: "There are no symptoms of aortic stenosis" and dismissed the subject with extreme brevity.[4] We now have a more mechanical and less philosophical view of the heart, at least as far as valve disease is concerned. Relief of aortic stenosis improves symptoms, lengthens expectation of life,[5] and, even in those who do not complain of symptoms because the progress of their disability is insidious, valve replacement improves well-being and exercise tolerance. The point at issue is whether these benefits can also be obtained by balloon dilatation.[6] To the surgeon at least, it seems inherently unlikely. Video pictures (screened in 1988 at the British Cardiac Society meeting) of balloon dilatation performed in vitro on excised valves did nothing to counter my prejudice against this procedure.[7]

Brock led his contemporaries in attempts at closed aortic valvotomy and reported on 20 cases to the British Cardiac Society in 1954[8] but the results were mechanically unsatisfactory. Relief of obstruction may result from commissurotomy of an otherwise flexible valve (as in mitral stenosis) but the type of aortic valve that we remove in elderly patients is usually a craggy, rigid, and completely hopeless looking structure. But to reject balloon dilatation because in theory we do not think that it should work is to treat enterprising cardiologists in the way Souttar was treated by his colleagues.

Protagonists of balloon dilatation report benefit not attended by the level of mortality that one might have feared. In recent series that included some severely compromised patients[9–13] there were eight early deaths in 130 patients (70% confidence interval 4%–9%). This resembles the surgical (30 day) mortality which has varied between 4% and 6% between 1980 and 1985. Stroke is rare, although vascular damage at the site of access was not uncommon. Getting the patient out of the catheter laboratory alive and without a stroke is creditable, but a more useful index of mortality is the proportion of patients that are alive at a year. In one series the mortality was 28% at six months and 55% at a year.[12] Sprigings *et al* reported that less than half their patients were alive at a year.[13]

We also need to look carefully at the indices of success. The mean of the mean gradients falls by 31–41%, but the truth might be hidden

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in all that averaging. First of all, the arithmetic mean is inappropriate for skewed data. In two papers where the raw data are available[9,10] the preoperative mean gradients (86 and 84 mm Hg) are influenced by high outliers, and the medians (70 and 75 mm Hg) may be more representative. More serious is the exaggeration of results by the enthusiastic use of p values. Any test of difference, and the popular paired *t* test has been used repeatedly both for gradient and valve area, will be highly "significant", however small the improvement, provided all changes are in the same direction,[14,15] which must be the case unless a substantial proportion of the valves become worse. Thus all the statements that the gradient is significantly reduced, or the valve area is significantly increased mean very little. The preoperative valve areas are estimated to be, on average, 0·5 cm^2. The median valve area immediately after the procedure was 0·73 cm^2 in 100 cases from five studies[9–11,13,16] so although the p value for difference may have been $<0{\cdot}0001$[11] or even $<0{\cdot}000001$[10] by the paired *t* test, only 10 out of 100 cases had an aortic valve area of more than 1·0 cm^2 after dilatation. Most still had severe aortic stenosis. The result for 442 patients in the French register was similar, with an increase in valve area from 0·48 cm^2 to 0·80 cm^2.[17] Furthermore, these are early estimates of increased valve area which are not reproducible if the patient is restudied a week or more later.[13,16,18] Whether this is because of loss of actual benefit[18] or because the early measurements are inaccurate because of reduced flow is a matter of conjecture.

So we are no longer discussing a means of relieving aortic stenosis but, at best, of creating a margin of benefit sufficient for some specific purpose. For example, if a patient with aortic stenosis needs other emergency surgery balloon dilatation may produce enough improvement to permit anaesthesia, and this seems to be a reasonable approach.[19,20] Also improvement in a patient with very low cardiac output may make valve replacement safer.[21] Balloon dilatation does not seem to be justified in patients with terminal carcinoma[9] whose life it might extend long enough for them to die of something worse. The risks of balloon dilatation are higher in the elderly[21] and age is not in itself a barrier to definitive valve replacement if relief of stenosis is justified on other grounds.[21–24] In one of the earlier series five out of eight patients subsequently had surgery[25] so there is some leeway in judging suitability for operation.

In fairness, I must say that all the groups that I have quoted were very guarded in their remarks about balloon dilatation and indicated the relatively poor relief of stenosis and the short duration of benefit.[13,16,18] Only two of the 32 patients studied by Sprigings *et al* had lasting benefit.[13] It seems that the indications are already limited and enthusiasm is on the wane.

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VIEWPOINT

Balloon dilatation of the aortic valve in adults: a physician's view

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The treatment of symptomatic aortic stenosis in elderly patients by percutaneous balloon dilatation was introduced by Cribier in 1985 although the procedure had already been used successfully in children with stenosis of the pulmonary and aortic valves. Until 1985 the only effective treatment was surgery—aortic valvotomy or aortic valve replacement. In the elderly, aortic valve replacement is associated with considerable morbidity and perioperative mortality ranging from 3%[1] to 18%[2] with even higher rates (23%) in patients who are more than 75 years old.[3] Most of the reported series were completed some time ago and may not reflect current surgical practice. But patients in any surgical series have been selected because they are a good risk; whereas balloon dilatation of the aortic valve is generally performed in patients who are regarded as high risk candidates for surgery or who have been refused surgical treatment. The main purpose of invasive treatment is to relieve symptoms; one year survival of untreated elderly patients is as low as 57%,[4] and even after successful valve replacement or successful balloon dilatation survival cannot be expected to be greatly improved.

Percutaneous balloon dilatation of the aortic valve is currently performed by various related techniques that have become increasingly refined. The technique is simple to perform but as with other interventional procedures the results and complication rates reflect the experience of the operator. This point must be taken into account in interpreting some of the reported series and in assessing the value of the technique. For example in two of the larger series of patients treated by balloon dilatation, one from Europe[5] and the other from the United States,[6] mean aortic valve areas increased from 0·49 to 0·93 cm^2 and from 0·6 to 0·9 cm^2, with 41% and 19% of patients having an aortic valve area greater than 1 cm^2, a value widely associated with a good chance of a favourable medium term outcome. In contrast some series report valve increases as small as from 0·41 to 0·60 cm^2, which cannot be expected to produce sustained haemodynamic improvement. These small increases may be related to the use of a single, possibly undersized, balloon.

Reliable assessment of the results is hampered by the lack of a sufficiently precise method of assessment. Echocardiography including Doppler assessment is not sufficiently objective and variations in both the pressure gradient and the calculated valve area are exaggerated by the large changes in flow and filling pressures that occur during the procedure. We need a better method of distinguishing between a poor result and restenosis of the valve.

The mechanism by which dilatation achieves the improvement is not well understood. In elderly patients aortic stenosis is usually caused by degenerative changes. The valve leaflets are rigid, often with extensive calcification. In general commissural fusion is not an important factor. Therefore the commissural splitting produced by balloon dilatation, which is known to be important in rheumatic aortic stenosis, is of little relevance in calcific aortic stenosis. The most commonly accepted explanation for the improvement after balloon dilatation, which is based on limited experimental evidence, is that a combination of stretching of the aortic valve ring and fracture of the calcified "skeleton" of the valve increases the mobility of the valve leaflets. In the absence of any more dramatic mechanism of action it is perhaps not surprising that only relatively modest increases in valve area are recorded. None the less, because of the curvilinear relation between aortic valve area and valve gradient small increases in valve area produce important haemodynamic and functional improvement.

Balloon dilatation of the aortic valve is associated with a mortality of about 1% and an in-hospital mortality of <5% (most deaths are caused by progressive heart failure). Minor complications of gaining arterial access at the femoral puncture site are common and because they may lead to a general anaesthetic being required in frail elderly patients their effects on outcome should not be underestimated. Complications—such as stroke, myocardial infarction, tamponade, and aortic regurgitation—are less frequent but not insignificant. If the procedure were curative the complication rate would be acceptable, but long term follow up showed that the short term benefits are not well maintained. A study by Commeau *et al* found that at repeat cardiac catheterisation eight days after dilatation most of the initial benefit had been lost though there was still significant improvement over values before dilatation.[7] Most studies show that at six months only 50% of patients continue to benefit from the procedure and in selected patients the mortality at one year may be no different from that in untreated patients.[8] However, comparisons of this type, of the total population with high risk subgroups, may give rise to misleading conclusions and this comment is relevant to all comparisons of operations of the aortic valve. Most of our patients with recurrence of symptoms were operated on and, despite initial reservations by the surgeons, all have done well.[9] There is little doubt that the introduction of percutaneous balloon dilatation of the aortic valve has stimulated the surgeons to review their indications for aortic valve replacement in the elderly, and that this has resulted in a less conservative approach to these patients in many centres.

The technique of percutaneous balloon dilatation of the aortic valve is still being developed. In children or in patients with small aortic roots it has been shown to be of value. The group of patients who are likely to benefit most from this procedure are the thousands of younger patients in developing countries who die each year of untreated rheumatic aortic stenosis. Most of these patients do not have the opportunity to have surgical treatment and this is unlikely to change soon. The use of imaging techniques such as intravascular ultrasound, which is capable of producing high resolution images of valve leaflets, may allow more effective non-surgical treatment. The ability to perform selective commissurotomy and immediately to assess both the functional result and the anatomical result will lead to renewed interest in balloon dilatation.

Currently balloon dilatation can be expected to produce immediate symptomatic relief with acceptable complication rates in most patients. Long term success is low in the elderly and the technique cannot be considered as an alternative in those who are suitable candidates for surgery. Appropriate patient selection is crucial and the procedure is perhaps most useful in providing a "bridge" to surgery. It should be performed in a limited number of centres by experienced operators who are able to maintain their expertise by operating regularly.

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Relation of filling pattern to diastolic function in severe left ventricular disease

Kelvin S K Ng, Derek G Gibson

Abstract

M mode and Doppler echocardiograms, apex cardiograms, and phonocardiograms were recorded in 50 patients with severe ventricular disease of varying aetiology to examine how left ventricular filling is disturbed by cavity dilatation. The size of the left ventricular cavity was increased in all with a mean (SD) transverse diameter of 7·2 (0·8) cm at end diastole and 6·3 (0·8) cm at end systole. All were in sinus rhythm and 35 had functional mitral regurgitation. In nine patients, in whom filling period was < 170 ms, transmitral flow showed only a single peak, representing summation. In the remainder there was a strikingly bimodal distribution of filling pattern. In 12 the ventricle filled dominantly with atrial systole (A fillers). Isovolumic relaxation was long (75 (35) ms) and wall motion incoordinate; mitral regurgitation was present in only one. In most (29) the left ventricle filled predominantly during early diastole (E fillers). Mitral regurgitation, which was present in 26, was much more common than in the A fillers, while the isovolumic relaxation time (10 (24) ms) was much shorter and the normal phase relations between flow velocity and wall motion were lost. In 24 E fillers no atrial flow was detected. In four there was no evidence of any mechanical activity, suggesting "atrial failure". In 20, either the apex cardiogram or the mitral echogram showed an A wave, implying that atrial contraction had occurred but had failed to cause transmitral flow, showing that ventricular filling was fundamentally disturbed in late diastole. A series of discrete abnormalities of filling, beyond those shown by Doppler alone, could thus be detected in this apparently homogeneous patient group by a combination of non-invasive methods. The presence and nature of these abnormalities may shed light on underlying physiological disturbances.

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Myocardial anatomy is abnormal and function disturbed when the cavity of the left ventricle is dilated. The amplitude of endocardial motion and in particular the extent of wall thickening are uniformly and strikingly reduced, and mitral regurgitation is often present. Although these findings are usually attributed to impaired systolic function,[1] they might also interfere with ventricular filling in ways that could throw light on the underlying abnormalities of diastole. We therefore recorded transmitral flow velocity patterns in a large series of these patients and considered them not on their own but with other non-invasive measures of diastolic function to see how they are related to one another. We also examined how the different filling patterns are distributed across the group as a whole, and correlated these patterns with other manifestations of disease.

Patients and methods

We studied the records of 50 patients with cavity dilatation caused by severe left ventricular disease. All had had at least one attack of pulmonary oedema and ten of the 15 under the age of 55 subsequently underwent cardiac transplantation. In all the patients the left ventricular end diastolic dimension, as measured by M mode echocardiography, was > 6 cm; fractional shortening was < 25%, and the ventricular posterior wall thicknesses were < 1·2 cm at end diastole. Their age ranged from 12 to 80. In 20 the underlying diagnosis was coronary artery disease, established by coronary arteriography or at necropsy or transplantation. Eleven had dilated cardiomyopathy with normal coronary arteriograms. In six patients left ventricular disease could be related to sarcoidosis, polyarteritis nodosa, disseminated lupus erythematosis, irradiation, Becker's muscular dystrophy, or eosinophilic heart disease in one case each. In thirteen patients, there was no clinical indication for coronary arteriography, so we were unable to exclude coronary artery disease (table 1). No patient had important organic valve disease or regional disturbance of left ventricular wall motion shown by cross sectional echocardiography. At the time of the study, nine patients were taking a digitalis preparation, 27 an angiotensin converting enzyme inhibitor, six some other vasodilator, and all but four a diuretic.

ECHOCARDIOGRAMS

The recording of M mode echocardiograms was guided by the cross sectional display. Those of the left ventricular cavity were taken at the level of the tips of the papillary muscles and showed clear continuous echoes from the left side of the septum and the endocardial surface of the posterior left ventricular wall. Additional records were made at the level of the mitral valve cusps to show their motion throughout diastole and particularly the time they separated at the onset of rapid filling and

Table 1 Clinical details

	E fillers (n = 29)	*Summation (n = 9)*	*A fillers (n = 12)*
Age (mean (SD)) yr	52 (18)	56 (10)	64 (18)
Sex (male)	24	6	9
Aetiology:			
Coronary artery disease	14	3	3
Dilated cardiomyopathy	6	1	4
Other specific disease	2	2	2
Not established	7	3	3
Drugs			
Digitalis	5	1	3
Diuretic	27	7	12
ACE inhibitor	19	3	5
Other vasodilator	3	1	2

ACE, angiotensin converting enzyme.

during atrial systole. We used aortic echograms showing the time of apposition of the valve cusps at the end of ejection to identify the aortic component of the second heart sound (A_2) on a simultaneous phonocardiogram and also to assess left atrial transverse dimension and aortic root motion.

We recorded apex cardiograms from the point of maximal impulse using a Cambridge Instruments transducer with a time constant of 4 s. Doppler recordings of mitral flow velocity were made with a Doptek Spectrascan and a 2 MHz transducer. We identified peak transmitral velocity using the continuous mode and then recorded in pulsed mode with a 3 mm gate and a 250 Hz wall filter. Mitral regurgitant flow was identified and recorded in continuous mode. All records were taken at a paper speed of 10 cm/s, with simultaneous phonocardiograms and electrocardiograms; the latter were amplified (if necessary) to show P waves clearly.

MEASUREMENTS

M mode echocardiograms

We measured end diastolic and end systolic dimensions and septal and posterior wall thicknesses from their leading edges at the time of onset of the Q wave and A_2 respectively. We also measured the time intervals from A_2 and minimum cavity dimension to mitral valve opening; the interval from A_2 to mitral valve opening was taken as the isovolumic relaxation time. On the mitral echogram we considered that the cusps separated during atrial systole only when they unequivocally started to move apart after the P wave of the succeeding beat.

We digitised M mode echocardiograms of the left ventricular cavity[2] to give peak rates of change of transverse dimension and posterior wall thickness during diastole. We also measured the interval from A_2 to peak rate of dimension increase (fig 1). Because the rates of change of left ventricular wall thickness were very low (3·6 (2·0) cm/s) and time intervals related to events on these traces were unreproducible we did not use them.

APEX CARDIOGRAM

We measured the relative height of the A wave as the ratio of the increase during atrial systole to the total excursion during the cardiac cycle, identifying the onset of the A wave as the start of increased rate of rise on the apex cardiogram occurring after the P wave.

DOPPLER TRACES

We identified an E wave on the Doppler flow-velocity trace as a peak occurring after mitral opening but before the onset of the P wave of the succeeding beat (fig 2a) and we measured the interval from A_2 to the time that the peak flow velocity was registered (fig 1). If the E wave was dominant we classified such patients as E fillers. We identified an A wave as occurring after the P wave of the succeeding beat and as being preceded either by an E peak or by an interval of low flow after mitral valve opening (fig 1b). We classified patients with a dominant A wave as A fillers. If only one peak was present, starting immediately after mitral opening but after the P wave of the succeeding beat, we classified the filling pattern as summation (fig 2c). To distinguish a summation wave

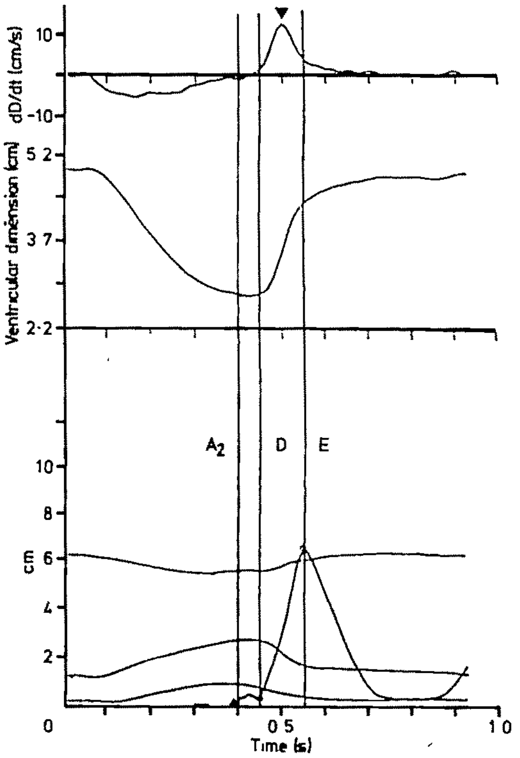
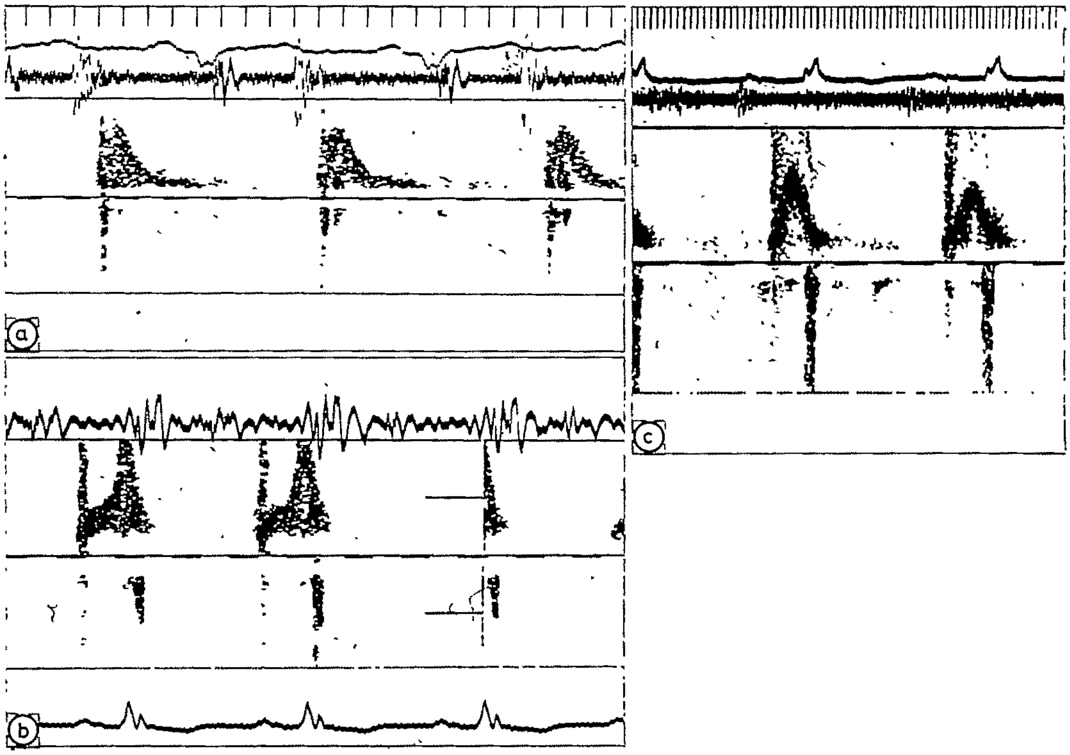


Figure 1 Interrelations of early diastolic events derived from digitised M mode echocardiogram of the left ventricular cavity and transmitral flow velocity record. The lowest panel represents left ventricular wall echoes with Doppler trace superimposed. The middle trace gives the ventricular dimension, and the top trace, the rate of change of dimension (dD/dt). Aortic closure (A_2) normally precedes minimum cavity dimension (D), which itself is synchronous with mitral valve opening. Peak transmitral flow velocity (E) characteristically follows peak dD/dt (marked with an arrow) by 50 (15) ms.

Figure 2 (a) Transmitral flow velocity trace showing early diastolic filling from a patient in sinus rhythm but without a perceptible A wave. Full scale deflection on Doppler 4 kHz. Time marker 0·10 s. (b) Transmitral flow velocity trace showing a dominant A wave. There is no clear early diastolic peak. Full scale deflection on Doppler 2 kHz. (c) Transmitral flow velocity trace showing a summation filling pattern. There is a single peak, with its onset early in diastole but after the P wave of the succeeding beat. Full scale deflection of Doppler 4 kHz.



caused by atrial systole from an E wave fortuitously following the P wave of the next beat we estimated the interval from the onset of P wave to the peak of the A wave in the A fillers. We quantified the filling pattern in the E and A fillers by calculating the ratio A/(A+E), where A and E represent peak flow velocities occurring with A and E waves respectively. This has a value of 0 when filling is exclusively with an E wave, 1 when it is exclusively with an A wave, and an intermediate value when both waves are present. We preferred to use this ratio rather than the simpler ratio of A/E, which behaves non-linearly and becomes undefined when filling is exclusively atrial.

If mitral regurgitation was present we measured the intervals from A_2 to the end of regurgitation and the total duration of the regurgitation.[3] We derived the time between the pulses of mitral regurgitation as the difference between RR interval and the duration of the mitral regurgitation. When mitral regurgitation was present, we calculated effective filling time as we have described elsewhere[3]: otherwise we took it as the total time that the mitral valve was open.

STATISTICAL ANALYSIS

We used mean (SD) throughout. We investigated the statistical significance of differences between means by Student's *t* test and the differences of incidence between groups by Fisher's exact probability test. We used the Kolmogorov-Smirnov test to examine possible departures from a unimodal distribution.

Results

FILLING PATTERN AND ITS DISTRIBUTION

Of the patients studied, nine showed a summation pattern of filling, while in the remainder (41) all waves could be identified as A or E. We constructed a frequency histogram for values of the ratio A/(A + E) in these 41 (fig 3). They were not unimodally distributed; there are two peaks, one corresponding to E filling with a value of 0–0·2, and the second to A filling with values between 0·8 and 1·0. This departure from a unimodal distribution is very significant ($p < 0.001$). There were three groups: summation fillers, A fillers, and E fillers. Table 1 gives the details of age, sex, aetiology, and treatment in the three groups. A fillers tended to be older than those in the other two groups, but this difference was not statistically significant. Aetiology and drug treatment were distributed uniformly.

CHARACTERISTICS OF INDIVIDUAL GROUPS

Table 2 sets out the general characteristics of the three groups. Left ventricular cavity dimensions were the same in all three and were

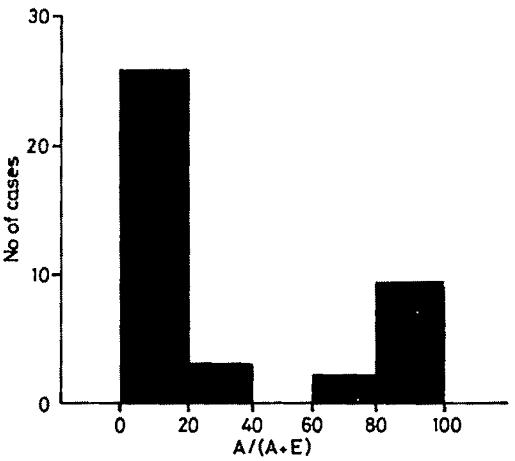


Figure 3 Histogram showing distribution of values of the ratio A/(A+E), where A and E are peak velocities of A and E waves respectively. Patients with a summation filling pattern are excluded. Note the bimodal distribution.

Table 2 Left ventricular filling pattern (mean (1 SD))

	E fillers	*A fillers*	*Summation*	*Significance of difference* *E v A fillers*	 *E v Sum fillers*	 *A v Sum fillers*
Left ventricle						
End diastolic dimension (cm)	7·2 (0·75)	7·4 (0·7)	7·0 (1·1)	NS	NS	NS
End systolic dimension (cm)	6·4 (0·9)	6·3 (0·8)	7·0 (1·1)	NS	NS	NS
Left atrium:						
Dimension (cm)	4·2 (0·5)	3·1 (0·8)	3·2 (0·2)	0·05	0·05	NS
Total amplitude of motion (mm)	4·0 (2)	5·0 (3)	4·0 (2)	NS	NS	NS
Atrial systole—amplitude (mm)	0·6 (1·2)	3·0 (2)	—	0·01	—	—
RR interval (ms)	730 (20)	750 (15)	530 (80)	NS	0·01	0·01
Left ventricular filling time (ms)	300 (70)	320 (75)	130 (40)	NS	0·01	0·01
A_2 to mitral valve opening (ms)	10 (24)	75 (35)	10 (20)	0·01	NS	0·01
Minimum D to mitral opening (ms)	6 (39)	85 (50)	10 (20)	0·01	NS	0·01
Mitral regurgitation (no)	26	1	8	0·01	NS	0·01
Tricuspid regurgitation (no)	5	3	2	NS	NS	NS
Aortic regurgitation (no)	1	2	0	NS	NS	NS

Sum, summation; D, dimension.

unaffected by whether or not mitral regurgitation was present. In the E fillers isovolumic relaxation (A_2 to mitral opening) was very short. Mitral valve opening was effectively synchronous with minimum cavity dimension, and peak rate of dimension increase was synchronous with peak inflow velocity, rather than preceding it as is normal. RR interval and left ventricular filling time were essentially the same as for the A fillers, but the left atrium was larger and mitral regurgitation was detected much more often. In 24 of these patients there was no discernible A wave on the Doppler flow velocity trace; in four of these atrial activity was also absent from the apex cardiogram and mitral echogram, but in the remainder (20) a clear A wave was present on one or both of these records (fig 4).

The isovolumic relaxation time was very much longer in A fillers than in E fillers and mitral opening greatly delayed with respect to minimum dimension. The left atrial dimension was smaller but the component of dimension change occurring during left atrial systole was larger. Though mitral regurgitation was much less common than in the E fillers, the incidence of aortic and tricuspid regurgitation was essentially the same.

Summation fillers resembled E fillers in that the isovolumic relaxation time was short; mitral opening was synchronous with minimum cavity dimension and peak rate of dimension increase was synchronous with peak transmitral inflow velocity. The RR interval was short and the effective filling time was greatly reduced to 50–170 ms, while the shortest value seen in either of the other groups was 230 ms. In the A fillers the mean interval from the onset of the P wave to peak atrial flow velocity was 190 (20) ms, giving a 95% confidence interval with a lower value of 150 ms. In five of the summation fillers the interval was less than this, showing that the single peak was effectively an E wave; in the remainder, in whom the interval was greater, we could not determine its origin.

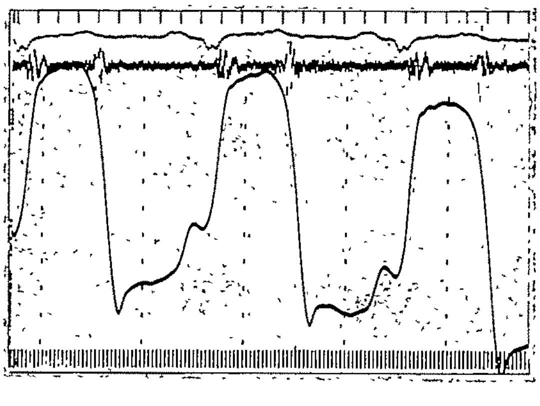


Figure 4 Apex cardiogram from the patient whose Doppler transmitral flow velocity trace is shown in fig 2a. Note that there is a clear A wave on this trace.

Discussion

A dilated cavity with reduced wall motion is the end stage of many types of left ventricular disease. Whatever the underlying cause, the clinical picture is almost identical in every case and the prognosis uniformly poor. It is generally believed that left ventricular systolic function is globally impaired[1] and that this leads to the characteristic changes in ejection, with the aortic valve opening late and ejection time itself being shortened.[4] Diastolic function may also be abnormal in these patients[5 6] but, surprisingly, transmitral flow velocity patterns are frequently reported as normal,[7–9] a discrepancy we sought to explain.

Many have drawn conclusions about left ventricular diastolic function from the filling pattern as displayed on the Doppler flow-velocity trace[10 11] and in particular from the relative heights of the E and A waves. Yet this method requires not only that patients are in sinus rhythm but also that both peaks are recognisable in the flow velocity record. Although our patients were all in sinus rhythm, in nine we found only a single peak. We could not always be certain whether this single peak represented early diastolic or atrial filling. Whatever its exact genesis, the shape of the single peak (Fig 2c) showed that its time integral was the maximum that would be possible with the observed acceleration and deceleration rates within the short filling period. We concluded, therefore, that this characteristic pattern was not due simply to low cardiac output, but arose when stroke volume was directly limited by external constraints on the time available for forward mitral flow. In a second group of patients, the ventricle filled either dominantly or completely with atrial systole. They differed from the summation fillers in that filling time was much longer and either an E wave was present or there was a discrete interval after mitral valve opening when transmitral flow could not be detected. In the third and commonest filling pattern, however, the higher velocity occurred early during diastole, before the P wave of the succeeding beat, and the atrial peak was low or absent. Surprisingly, E and A filling patterns did not simply represent the ends of a single continuum because the distribution of the relative heights of the two waves in the patients studied was strikingly bimodal. If mitral flow was not limited by a short filling period, therefore, it tended to occur either early or late in diastole. The normal finding of comparable E and A wave velocities was conspicuously absent in the group of patients with end stage disease that we studied.

Bimodal distribution of any variable within a homogeneous group of patients is unusual and must be explained. In ours it was not caused by differences in age, sex, aetiology, or treatment, nor was it related to cavity size, wall thickness, or shortening fraction. In more general terms, however, the two groups arose from loss of the A wave in the E fillers, and loss of early diastolic flow in the A fillers. The A fillers differed from E fillers in that isovolumic relaxation time was longer and wall motion during this period was incoordinate, as shown by the delay in mitral opening with respect to minimum cavity dimension. We have previously suggested that rapid early diastolic filling depends on the integrity of posterior wall thinning and its relation to mitral valve opening.[12] If either of these are lost because of incoordination, the early diastolic filling rate will be reduced—as we have previously shown by angiography in patients with coronary artery disease.[13]

Dominant early diastolic filling is associated with mitral regurgitation[7-9] and it has been suggested that volume overload or a high left atrial pressure may "normalise" the filling pattern. While we agree that the Doppler pattern, considered on its own, was apparently normal in some of our patients, this did not apply to other aspects of diastolic function. In the normal subject peak filling rate lags behind the peak rate of dimension increase by approximately 50 ms[14] (fig 1). We attribute this delay to the effect of restoring forces within the ventricle and have noted its loss in patients with severe mitral regurgitation. In E fillers also, the normal phase relation between transmitral flow velocity and dimension change was lost; while the Doppler pattern was apparently normal the mechanism by which it was brought about was not. This effect seems to have been the result of filling being brought about directly by a high left atrial pressure rather than being mediated by normal restoring forces. Loss of these forces would be expected because wall thinning during early diastole was so strikingly reduced,[12] while the abnormally short isovolumic relaxation time made a high left atrial pressure very likely.[15] The mitral regurgitation itself put no perceptible volume load on the left ventricle, since overall changes in atrial and ventricular dimension were similar whether or not it was present. Flow velocity, however, is determined by pressure gradient and only indirectly by stroke volume. A minor degree of mitral regurgitation will cause a considerable increase in pressure if the atrium is non-compliant.

An even more striking abnormality was the frequent loss of the A wave in the E fillers. It seems unlikely that we simply failed to detect an atrial flow signal in these patients because we specifically sought it with continuous wave as well as pulsed Doppler and because the fall in left atrial dimension during atrial systole was much smaller than in the A fillers. In a minority we found no evidence of any mechanical activity of the left atrium although all were in sinus rhythm. Mechanical atrial activity may be lost for short periods after DC conversion of atrial fibrillation,[16] but the idea that "atrial failure" might persist chronically has been little considered. In most patients in whom no atrial flow could be detected we found collateral evidence of atrial mechanical activity either on the apex cardiogram or the mitral echogram. We were thus forced to conclude that even with an appropriately timed atrial contraction, transmitral blood flow did not occur. This implies loss of ventricular compliance, which might be the result of intrinsic myocardial disease, disturbed myocardial architecture, or pericardial restraint. One does not need to know its exact mechanism to deduce that in these patients there must be a major disturbance of filling in late diastole. End diastolic volume apparently becomes fixed, so that after early diastolic inflow these ventricles effectively become "unfillable".

The present study has several obvious limitations. All the patients had had pulmonary oedema at some time, and many of the younger ones were being considered for cardiac transplantation. They are thus likely to have had more severe disease than those in previous series.[7-9] They were studied at a single stage in their clinical course, and we do not know how the filling pattern might change with time. All were taking treatment, which was in no way standardised and with which we did not interfere. The study, however, was a retrospective one, so that our knowing the filling pattern could not have affected the way the information was collected. We investigated the possibility that apparent transmitral flow pattern might have depended on the transducer position or orientation but we were unable to find evidence of this. We used continuous wave Doppler to identify peak velocities before recording them in the pulsed mode, so that sampling depth was not a potential variable. Mitral regurgitation in such patients may occur through a localised jet, and thus detecting it might be unpredictable. However, such unpredictability would be random, and could not explain the large difference in incidence between E and A fillers. Detecting tricuspid regurgitation should be similarly limited, yet we found no comparable correlation.

Recognition of different filling patterns may help in the understanding of the pathophysiology and response to treatment of these patients. We have suggested that a filling time of 200 ms or less may of itself limit filling[3]; a summation pattern on the Doppler seems a simple way of detecting limited filling time.

Reducing the heart rate, which prolongs the filling time, would thus seem useful; this effect may explain the effects of β blockers in some patients with dilated cardiomyopathy.[17] In most patients, however, the filling time did not seem to limit stroke volume, at any rate at rest, with transmitral flow occurring dominantly at its beginning (E fillers) or at its end (A fillers); a reduction in heart rate would be unlikely to increase cardiac output in these circumstances and might well reduce it when stroke volume is small and fixed. A fillers, however, are likely to be particularly sensitive to the effects of atrial systole, so that manoeuvres aimed at restoring or maintaining sinus rhythm would seem particularly justified. If the end diastolic volume is indeed fixed in most E fillers, as we suggest, a major mechanism of adapting to increasing venous return has been lost. Further, most of these patients had mitral regurgitation that was too mild to have significantly affected resistance to ejection. With end diastolic volume fixed and end systolic volume unaltered, any increase in regurgitant volume must lead to an equal drop in forward flow. If the resulting fall in myocardial perfusion were to make the mitral regurgitation itself even slightly more severe, a vicious cycle would be set up, causing forward output to fall progressively and providing a mechanism for sudden death quite independent of any electrical instability. From the clinical point of view, therefore, treatment should be aimed at reducing end systolic volume and mitral regurgitation; these effects are brought about most predictably by use of arterial vasodilators and diuretics. Increased venous return on its own, mediated for example by a venodilator, would probably be less useful in such patients. The need to reduce end systolic volume suggests an ancillary role for drugs with a positive inotropic action, quite independent of any effects that they may have on the force or velocity of contraction.

We conclude that the pattern of transmitral flow velocity is often apparently unaffected by severely disturbed diastolic function in patients with dilatation of the left ventricular cavity. We have seen the same effect in patients with left ventricular hypertrophy,[18] where the disturbances differ from those of cavity dilatation. Doppler estimates of transmitral flow alone cannot therefore be considered an adequate basis for assessing ventricular diastolic function. However, when Doppler is used with other non-invasive measurements, a series of abnormalities can be shown in patients with end stage left ventricular disease. Not only do these disturbances seem to shed light on some aspects of the disordered pathophysiology but also they suggest how treatment might be approached. If the same methods are used to follow the effects of interventions, more rational and individual management may be developed for this difficult group of patients.

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Functional importance of the long axis dynamics of the human left ventricle

Christopher J H Jones, Luciano Raposo, Derek G Gibson

Abstract

The role of longitudinally and circumferentially oriented fibres in left ventricular wall motion was examined by digitising echocardiograms of the mitral ring (whose motion reflects long axis change) and of the standard minor axis in 36 healthy individuals, 36 patients with coronary artery disease, 16 with left ventricular hypertrophy, 44 with mitral valve disease (24 of whom had undergone mitral valve replacement). In the controls long axis shortening significantly preceded minor axis shortening (mean (1 SD) difference 25 (40) ms) so that the minor axis increased more during isovolumic contraction (0·25 *v* 0·09 cm), indicating that the left ventricle became more spherical. Changes in the long and short axes were synchronous at end ejection and in early diastole in the controls. Epicardial excursion preceded endocardial excursion by 50 (20) ms at its peak. These time relations were consistently disturbed in all patient groups, irrespective of the extent of fractional shortening of the minor axis. The onset of long axis shortening was delayed, and this was often associated with premature shortening of the minor axis, the normal spherical shape change during isovolumic contraction was lost, and peak epicardial and endocardial changes became more synchronous. In patients with coronary disease these changes are the expected consequence of ischaemic injury to longitudinally orientated subendocardial fibres. In left ventricular hypertrophy their presence consistently showed systolic dysfunction when orthodox measures were still normal. They were more pronounced after mitral valve replacement when the papillary muscles had been sectioned; long axis shortening was reduced during systole and prolonged into early diastole, while normal shortening of the minor axis was maintained only by abnormal epicardial excursion.

Relations between long and short axis motion in healthy individuals are characteristic, and their loss is an early index of systolic ventricular disease. These disturbances precede changes in orthodox measures such as fractional shortening or peak velocity of circumferential fibre shortening.

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Anatomical studies[1,2] have shown longitudinal as well as circumferential fibres with a continuous variation in fibre angle across the left ventricular wall. The function of these longitudinal fibres has not been extensively studied. Because effective ventricular function during ejection and filling is likely to depend upon the coordinated action of all myocardial layers, we set out to study the timing and extent of changes in the long axis, comparing them with those of the minor axis in healthy controls and those with left ventricular disease. In addition, we investigated patients after mitral valve replacement where a component of the longitudinal fibres (the papillary muscles) had been sectioned.

Patients and methods

CONTROLS AND PATIENTS

Cross sectionally guided M mode echocardiograms were recorded and analysed in 36 patients with coronary artery disease, 16 with left ventricular hypertrophy, 44 patients with mitral valve disease (10 with rheumatic mitral stenosis before surgical treatment, 24 after mitral valve replacement, and 10 after mitral valve repair), and 36 healthy individuals aged 51 (12) years without clinical, cardiographic, or radiographic evidence of heart disease and with normal amplitude and timing of endocardial motion and normal mitral valve leaflet motion on standard short axis M mode echocardiography. Patients with coronary artery disease had presumed angina and were those referred for routine diagnostic angiography. This showed single vessel disease in five, double vessel disease in ten, and triple vessel disease in 21. Cavity size and fractional shortening on M mode echocardiography were normal in 22. Fractional shortening was <23% (the lower 95% confidence limit of normal) in the remainder.

Patients with left ventricular hypertrophy had septal or free wall thickening greater than 12 mm on M mode echocardiography (the upper limit of normal).[3] Three patients had hypertrophic cardiomyopathy; of the remainder with secondary hypertrophy, seven had aortic stenosis, three arterial hypertension, two had undergone aortic valve replacement, and one repair of coarctation. The patients with rheumatic mitral stenosis had thickened valve leaflets, a reduced diastolic closure rate, and increased mitral diastolic flow velocities detected by continuous wave Doppler. Mitral valve replacement had been undertaken in 18

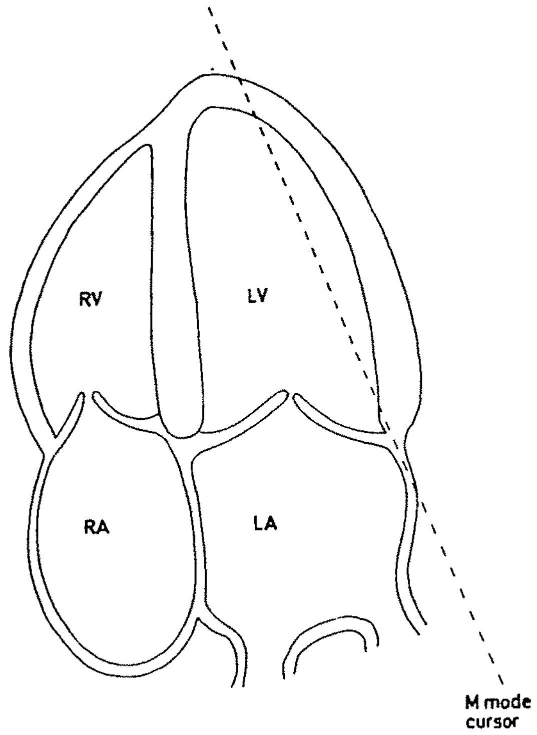


Figure 1 Schematic apical four chamber cross sectional view showing the M mode cursor positioned through the posterior aspect of the mitral ring. The cursor angulation was altered slightly to obtain M modes through the left ventricular apex.

patients for rheumatic mitral stenosis and in six for non-rheumatic mitral regurgitation. This was also the preoperative diagnosis in the 10 patients who had undergone mitral repair. All patients with mitral valve disease or replacement had normal left ventricular dimensions and fractional shortening. There was atrial fibrillation in five patients with mitral stenosis, 21 with mitral valve replacement, and five with mitral valve repair. All the remaining patients were in sinus rhythm.

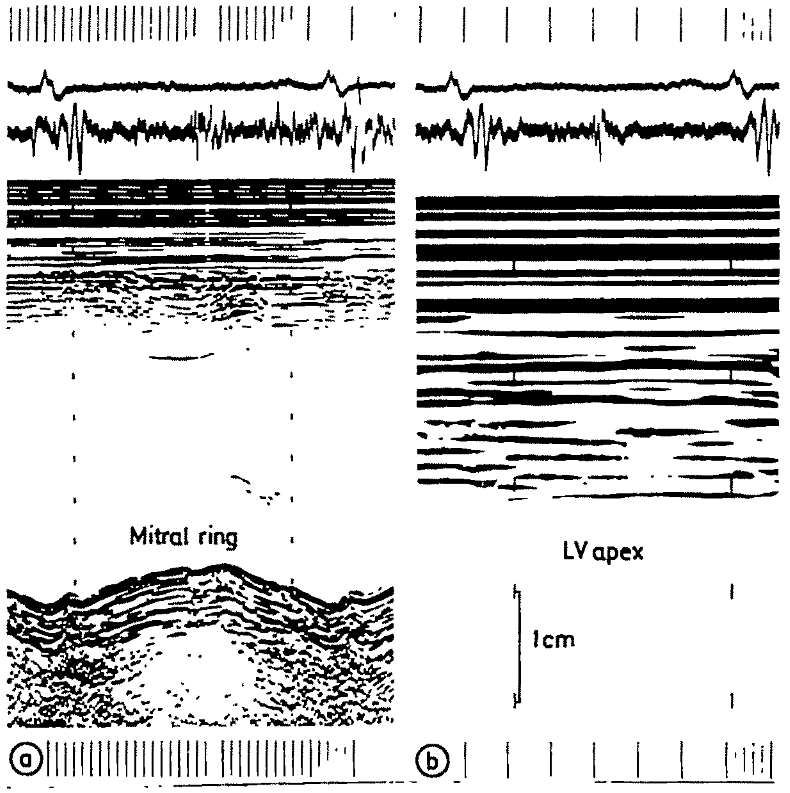


Figure 2 M mode echocardiograms of the mitral ring and left ventricular apex in a healthy control. The total amplitude of apical motion was less than 1 mm, indicating that changes in the position of the mitral ring reflect changes in left ventricular long axis dimension.

METHODS

M mode and cross sectional echocardiograms were obtained with the patient lying in the left lateral position with an 860C Imager with a 3·5 MHz mechanical transducer. M mode echocardiograms were recorded on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 100 mm/s with simultaneous electrocardiogram and phonocardiogram. Standard M mode echocardiograms of the left ventricular minor axis were recorded just below the level of the mitral valve leaflets. Cross sectional guided M mode echocardiograms of the left ventricular long axis were then obtained after longitudinal placement of an M mode cursor through the lateral aspect of the mitral valve ring, visualised on an apical four chamber cross sectional view (fig 1). Motion of the apex was recorded from the same position. Since the amplitude of movement was always less than 1 mm and since it showed no consistent relation to the electrocardiogram (fig 2), we disregarded it, and took overall shortening or lengthening of the long axis of the left ventricle as being reflected in corresponding motion of the mitral ring.

Echocardiograms were matched for the heart rate; the onset of the Q wave was used to time early systolic events and the first high frequency component of the aortic closure sound (A_2) was used to time early diastolic events. In the patients with atrial fibrillation RR intervals were matched to within 100 ms. The echocardiograms were digitised [4] and the following measurements were made as the mean value of three beats in each patient.

(*a*) Fractional shortening, the peak rate of fall of minor axis, and the peak rate of minor axis fibre shortening measured from the standard minor axis echocardiogram (calculated as the peak rate of minor axis change during systole normalised for end diastolic dimension).

(*b*) Time intervals from the Q wave to the onset of minor axis shortening and to the onset of long axis shortening (ms).

(*c*) Time intervals from the Q wave to the minimum minor axis and the minimum long axis (ms).

(*d*) The extent of minor and long axis change during the initial 100 ms from the Q wave (cm). Outward wall motion starting before the Q wave was considered to be the result of ventricular filling by atrial contraction and was excluded.

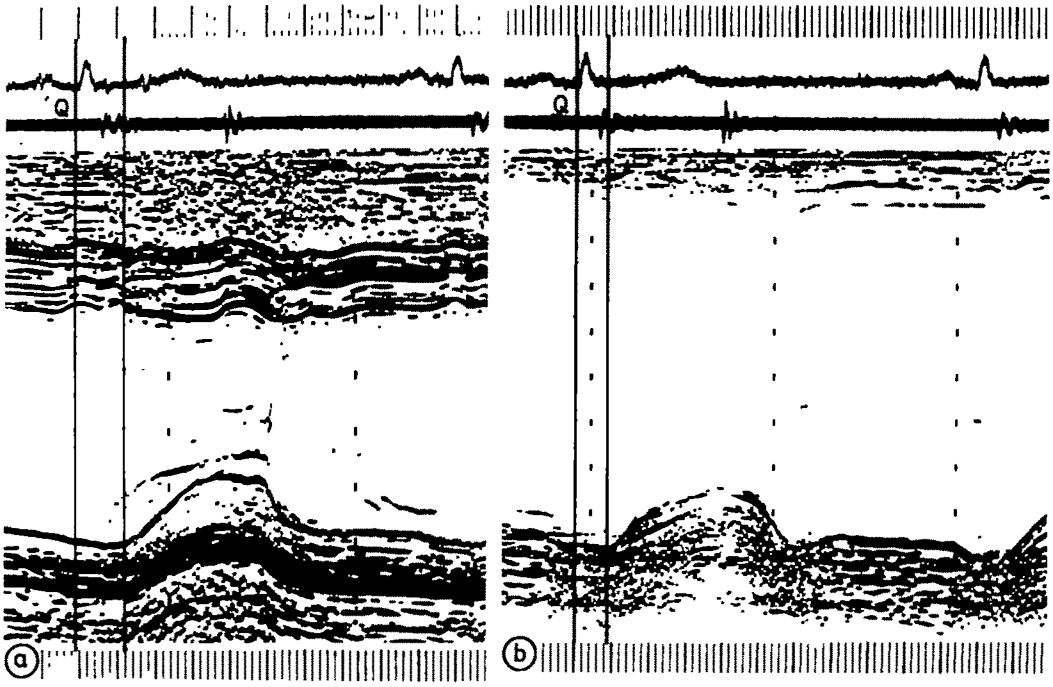
(*e*) The total amplitude of minor axis epicardial excursion (cm), and the time intervals from the Q wave to peak inward endocardial and epicardial excursion on the minor axis echocardiogram (cm).

(*f*) Total amplitude of long axis shortening (cm).

(*g*) Time intervals from A_2 to the peak rates of minor and long axis increase in early diastole (ms).

Mean values for each measurement obtained in the disease groups were derived and compared with values in healthy controls. Standard deviations were calculated and the significance of differences between means was assessed by *t* tests.

Figure 3 Minor (a) and long (b) axis echocardiograms of a control showing the earlier onset of long axis shortening, and normal posterior wall thickening. Changes in long and minor axes were synchronous at end ejection and in early diastole. The Q wave and the vertical lines indicate the onset of fibre shortening.



Results

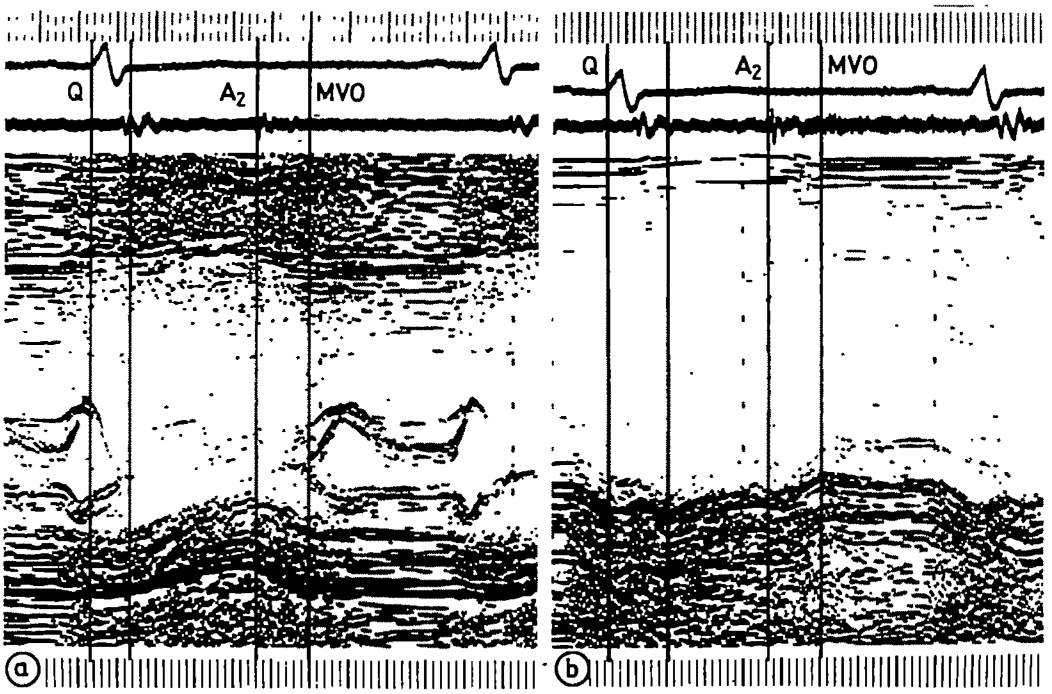
HEALTHY CONTROLS

In the controls (fig 3) fractional shortening was 33 (5)%, peak rate of dimension change was 9 (2·9) cm/s, and peak velocity of minor axis fibre shortening was 2·4 (0·5) cm/s. There was an initial increase in the long axis during isovolumic contraction of 0·09 (0·13) cm, significantly less than the corresponding change in the minor axis (0·25 (0·15) cm) ($p < 0·05$), so that the cavity became more spherical. Long axis shortening began 55 (40) ms after the Q wave and preceded shortening of the minor axis by 25 (40) ms ($p < 0·01$). Peak shortening of the two axes was effectively synchronous, occurring 410 (55) ms (long) and 430 (50) ms (minor) after the QRS complex ($p =$ NS). However, the timing of epicardial motion differed significantly from that of the endocardium. Peak inward motion of the epicardium consistently preceded that of the minor axis by 50 (20) ms, so that the epicardium moved outwards and the minor axis continued to shorten during isovolumic relaxation. The overall epicardial excursion was 0·5 (0·2) mm. The timing of peak rates of long and minor axis lengthening was effectively synchronous in early diastole, occurring 100 (25) ms and 90 (30) ms after A_2 respectively ($p =$ NS).

CORONARY ARTERY DISEASE

Early systolic events were significantly modified in patients with coronary artery disease (fig 4), whether or not standard measurements of left ventricular function were normal. Minor axis shortening started earlier than normal (55 (40) ms *v* 80 (40) ms after the Q wave, $p < 0·05$), while that of the long axis was delayed (85 (30) ms *v* 55

Figure 4 Minor (a) and long (b) axis echocardiograms of a patient with coronary disease and reduced fractional shortening. Long axis shortening was delayed beyond minor axis shortening so that the normal increase in the minor axis during isovolumic contraction was lost. Similar disturbances were seen in patients with normal fractional shortening. The abnormal change in shape caused by incoordinate relaxation was evident as an increase in the minor axis and a reduction in the long axis during a prolonged isovolumic period. A_2, aortic closure sound; MVO, mitral valve opening.



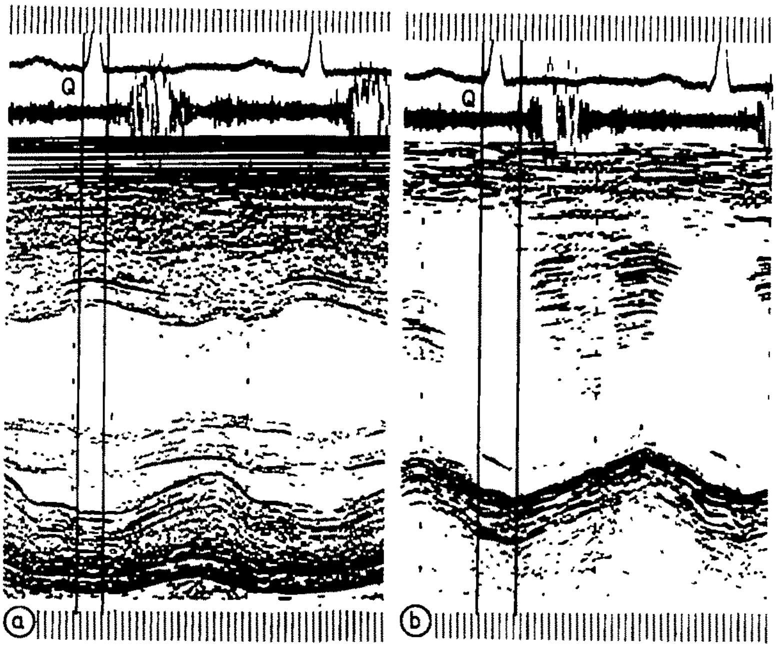


Figure 5 M mode echocardiograms showing delayed long axis (b) shortening with an abnormal shape change during isovolumic contraction despite normal fractional shortening on the minor axis (a) in a patient with aortic stenosis and left ventricular hypertrophy.

(40) ms, p < 0·01). The start of minor axis shortening thus preceded that of the long axis, rather than followed it as in the controls. At the same time the pattern during isovolumic contraction changed, with a fall in the extent of minor axis expansion from 0·25 (0·15) cm to 0·1 (0·1) cm (p < 0·05). The two axes were, however, synchronous at end ejection. The normal asynchrony seen between epicardial and minor axis motion was partly lost because peak epicardial displacement was delayed (difference 30 (20) ms, p < 0·01 *v* control), though the amplitude of epicardial excursion remained normal. During diastole the peak rates of increase of the long and minor axes were synchronous after A_2.

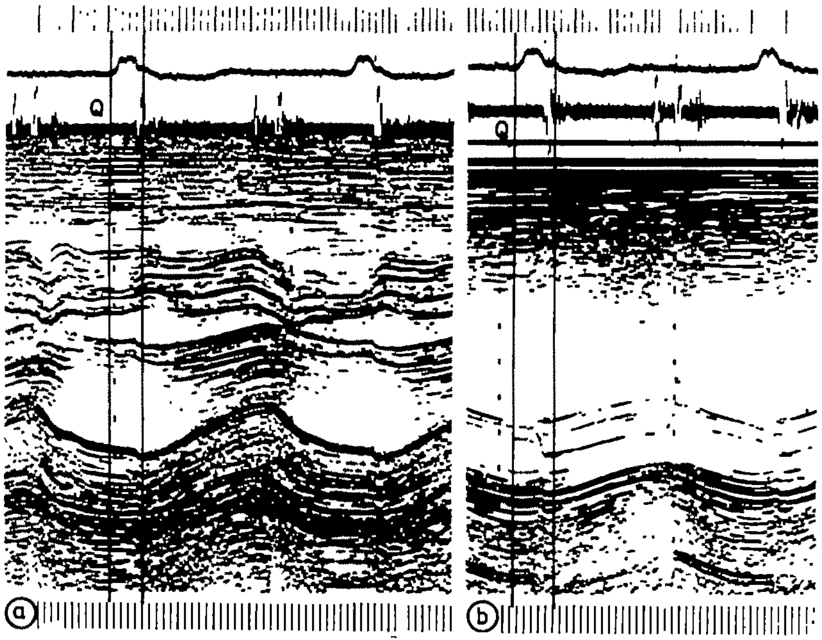


Figure 6 M mode echocardiograms showing characteristically delayed and diminished long axis shortening (b) in a patient after mitral valve replacement. Normal minor axis (a) endocardial motion is maintained only by increased epicardial excursion. Peak endocardial and epicardial motions were synchronous in this group.

LEFT VENTRICULAR HYPERTROPHY

Fractional shortening, peak rate of minor axis change, and peak velocity of circumferential fibre shortening were normal in the patients with left ventricular hypertrophy (30 (7)%, 8·3 (2·2) cm/s, and 2·6 (0·4) cm/s respectively, p = NS compared with controls). As with coronary artery disease, however, there was considerable initial systolic asynchrony (fig 5). Minor axis shortening again started earlier than normal with respect to the Q wave (60 (30) *v* 80 (40) ms, p < 0·05) and that of the long axis was delayed (95 (35) *v* 55 (40) ms, p < 0·01). Short axis expansion during isovolumic contraction was reduced (0·05 (0·1) *v* 0·25 (0·15) cm, p < 0·01) though long axis expansion was unaltered. However, despite their asynchronous onset peak shortening of the long and short axes was synchronous as was early diastolic filling. The extent of long axis shortening was normal. Peak epicardial excursion preceded peak endocardial excursion as in the controls (difference 45 (30) ms), and epicardial excursion itself was again normal.

MITRAL STENOSIS

Standard measures of left ventricular function were also normal in this group (fractional shortening 34 (8)%, peak rate of dimension change 7·5 (3·4) cm/s, and peak velocity of fibre shortening 2·3 (0·3) cm/s). However, the onset of long axis shortening was later (105 (35) *v* 55 (40) ms, p < 0·01) and its amplitude lower (1·0 (0·3) *v* 1·3 (0·2) cm, p < 0·05) in patients with mitral stenosis than in controls. The timing of the onset of minor axis shortening was normal (75 (25) ms after the Q wave, p = NS) and so shortening of the minor axis preceded that of the long axis. The long axis increased more than the minor axis during isovolumic contraction (0·4 (0·2) *v* 0·15 (0·2) cm, p < 0·01). Changes in the long and short axes were synchronous at end systole and during early diastole. Peak minor axis and epicardial shortening almost coincided (difference 20 (20) ms) although the amplitude of the epicardial excursion was normal.

MITRAL VALVE REPLACEMENT

Time relations were very abnormal after mitral valve replacement (fig 6). Long axis shortening was delayed (onset 95 (50) *v* 55 (40) ms, p < 0·01) and of reduced amplitude (0·9 (0·4) *v* 1·3 (0·2) cm, p < 0·01) while the amplitude of shortening of the minor axis was normal. The onset of minor axis shortening was much earlier than normal (45 (35) *v* 80 (40) ms, p < 0·01) without significant increase during isovolumic contraction (0·05 (0·1) *v* 0·25 (0·15) cm normal, p < 0·01). Wall motion was strikingly asynchronous at end systole, with peak minor axis shortening preceding that of the long axis by 70 (15) ms (p < 0·01), and during early diastole (peak lengthening rate minor axis 105 (25) ms *v* 195 (45) ms after A_2, p < 0·01). There was also a loss of the normal asynchrony across the ventricular wall, the difference between peak epicardial and minor axis shortening being only 10 (30) ms (p < 0·01). The normal amplitude of minor axis reduction was maintained by an increased amplitude of epicardial excursion (0·9 (0·3) *v* 0·5 (0·2) cm normal, $p < 0{\cdot}01$). These changes were again present despite normal fractional shortening, peak rate of dimension change, and peak velocity of fibre shortening (31 (6)%, 7·8 (2·2) cm/s, and 2·4 (0·4) cm/s respectively).

MITRAL VALVE REPAIR

In patients after mitral repair the onset and amplitude of long axis shortening were not significantly different from those in controls (onset 90 (70) *v* 60 (40) ms, p = NS) and events at end ejection and in early diastole were synchronous. The only disturbance in these patients was a slight increase in epicardial excursion (0·7 (0·2) *v* 0·5 (0·2) cm, $p < 0{\cdot}05$). Standard measures of left ventricular function were normal (fractional shortening 28 (6%), peak rate of dimension change 8·4 (1·8) cm/s, and peak velocity of fibre shortening 2 (0·5) cm/s).

Discussion

The way in which the functions of the longitudinally and circumferentially orientated myocardial fibres are interrelated to give a coordinated left ventricular contraction has been the subject of anatomical and physiological study for many decades. Straub[5] and subsequently Rushmer[6] showed that the longitudinal fibres started to shorten before those of the minor axis so that the cavity became more spherical—a sequence of events subsequently shown by Rankin *et al* to be related to the exact animal preparation used.[7] Another aspect of these interrelations has been investigated more recently—the extent to which longitudinal shortening contributes to wall thickening and thus to minor axis changes.[8,9] In spite of these studies, however, there has been little work on changes in the human long axis, and particularly on the effect of left ventricular disease. Because the apex of the left ventricle does not move significantly with respect to the transducer, long axis changes are reflected in movements of the mitral valve ring. Thus we have been able to study the relations between shortening of the long and minor axes of the left ventricle by simple echocardiographic techniques.

Our study confirmed previous experimental work by showing consistent differences in the timing and extent of long and minor axis shortening in controls. We showed the characteristic change in cavity shape during isovolumic contraction that occurs because shortening of the minor axis lags slightly behind that of the long axis. We also confirmed the presence of asynchrony across the posterior wall with the peak inward motion of the epicardium preceding that of the endocardium. This means that maximum long axis shortening, though synchronous with peak inward endocardial motion, is strikingly delayed with respect to that of the epicardium. These findings provide further examples of the regional non-uniformity of function that we and others have explored in the normal left ventricle.[10–12]

There were characteristic changes in these relations in patients with heart disease. With groups of widely differing aetiology, the normal sequence of early systolic events was consistently altered. Shortening of the minor axis started prematurely, longitudinal shortening was delayed, and changes in cavity shape during isovolumic contraction were abnormal. To test the hypothesis that these changes were the direct result of impaired function of the longitudinal fibres we studied patients after mitral valve replacement because in this operation the papillary muscles, a component of the longitudinally directed fibres, are cut. We found that wall motion was particularly abnormal in these patients. Not only was the normal early systolic sequence of events disrupted but also the extent of longitudinal shortening was reduced and the abnormal asynchrony between long and minor axes persisted throughout ejection and into early diastole. These changes were not a specific effect of cardiopulmonary bypass because they did not occur to the same extent after mitral valve repair, nor could they be attributed to a minor degree of mitral valve obstruction by the prosthesis because they were present to only a limited extent in cases of well developed mitral stenosis. We therefore attribute them directly to loss of a component of the longitudinally arranged muscle. Abnormal systolic performance has been lessened and survival improved after mitral valve surgery when the chordae tendineae were preserved[13–16]; however, longitudinal left ventricular function has not been examined specifically.

Our results also showed that a normal left ventricular shortening fraction after mitral valve replacement is maintained only by a very abnormal mechanism. The main basis of inward motion of the endocardium was changed: instead of being the effect of wall thickening as in the controls, it was the result of increased amplitude of motion of the epicardium. This fundamental change is exactly that predicted from anatomical studies[8,9,17] and is compatible with loss of the role of longitudinal fibre shortening in bringing about myocardial thickening, which determines the normal dynamics of the minor axis.

The results in patients with ischaemic heart disease were also instructive. Again abnormal long axis dynamics were associated with complex disturbances of ventricular function. The changes during isovolumic contraction caused by delayed longitudinal shortening resembled those seen in patients after mitral valve replacement. Epicardial amplitude remained normal but the normal lag in peak endocardial motion in relation to that of the epicardium was lost, particularly in patients in whom there was a change in cavity shape during diastole. This impairment of left ventricular longitudinal function in coronary disease is likely to have a basis in fibre architecture. Subepicardial and subendocardial fibre layers are longitudinally orientated whereas the middle layer is circumferentially arranged. Non-uniformity of fibre orientation was thus matched by a non-uniform susceptibility of the various layers to injury. Necropsy studies in patients with coronary disease show that the subendocardial fibres are more susceptible to diffuse ischaemic damage.[18] Subendocardial dysfunction is thus likely to affect selectively the longitudinally directed fibres and so to manifest itself as abnormal long axis shortening. Myocardial hypertrophy alone will also be associated with abnormal long axis dynamics if diffuse subendocardial damage reflects a relatively high risk of anoxia. Indeed we consistently found pronounced early systolic asynchrony and disorganised posterior wall thickening in patients with left ventricular hypertrophy, abnormalities that closely resemble those in patients with known coronary disease. They are the characteristic changes one would expect in the presence of disturbed shortening of longitudinal fibres.

Despite the obvious importance of coordinate contraction of all muscle layers in maintaining optimal ventricular function, the relative contributions of differently orientated myocardial fibres have been little studied in humans. Echocardiographic assessment of long and short axis changes allows an appreciation of the characteristic relations between the two. Their exact biological significance has still to be determined but we feel sure that it is closely related to the processes of energy transfer from the myocardium to the circulation. It also seems clear that loss of these close time relations may be an early sign of ventricular disease, occurring at a stage when fractional shortening is still maintained. There is still controversy about whether systolic left ventricular function is depressed in patients with left ventricular hypertrophy when cavity size and ejection fraction remain normal.[19] So it may be significant that we were consistently able to show systolic abnormalities in such patients, though they seemed to be confined to the function of the longitudinally directed fibres. Our findings may also shed light on the nature of the left ventricular disease after mitral valve replacement. Such disease is a major cause of long term morbidity and mortality after mitral valve replacement, although orthodox measures of left ventricular function may be normal in the early postoperative period.[20] It seems that there is a strong rational basis for any attempt to preserve the integrity of the mitral apparatus during operation. Finally, we regard our findings as a clinical vindication of the remarkable conclusions of Sir Arthur Keith, propounded over 70 years ago.[21] He commented on the interrelations between the "massive circular expelling coat", which he regarded as the agonist, and the longitudinal fibres (the antagonist) which supported them and prevented abnormal changes in cavity shape. Such changes, particularly when they occur in the two isovolumic periods, have been shown to cause striking loss of mechanical efficiency of ventricular pump function.[22] We feel that, taken together, these results again raise the question as to the best method of assessing left ventricular systolic function. As it becomes apparent that normal endocardial motion may be brought about by abnormal means we question whether attempts to summarise left ventricular systolic function as a single entity such as contractility or end systolic elastance are limiting. Rather, we suggest that the aim should be to assess the function of each of the anatomical components within the ventricles individually and to determine how these are integrated to give rise to the final pattern of wall motion.

C J H J is a British Heart Foundation Junior Research Fellow

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Haemodynamic changes caused by alteration of autonomic activity in patients with heart failure

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Abstract

In 14 patients with heart failure (New York Heart Association class 2–3) and sinus rhythm the carotid sinus baroreceptors were stimulated to induce a reflex mediated decrease of sympathetic efferent activity and a simultaneous increase in vagal tone. Five patients were in severe heart failure (New York Heart Association class 3) with raised plasma concentrations of noradrenaline at rest (2·99 (0·86) nmol/l (mean (SD)) and nine patients had less severe heart failure (class 2·2 (0·2)) and normal plasma concentrations of noradrenaline at rest. The haemodynamic responses during arterial baroreceptor stimulation were different in both groups. In all five patients with severe heart failure cardiac output increased whereas in the nine patients with less severe heart failure it was unchanged or decreased. The increase of cardiac output in the group with severe heart failure was solely the result of a significant increase of stroke volume index (by 9 (2) ml/m^2). In the nine patients with less severe heart failure stroke volume remained unchanged but heart rate decreased significantly by 7 (2) beats/min during baroreceptor stimulation.

These data show that an integrated change of autonomic activity consisting of a decrease in sympathetic tone and an increase in vagal activity leads to an increase of stroke volume in patients with severe heart failure and hence to haemodynamic improvement.

In patients with heart failure sympathetic tone is increased and parasympathetic activity is attenuated.[1–3] As a consequence of the increased activity of vasopressor systems the total peripheral vascular resistance is raised and may contribute to a progressive deterioration of myocardial pump function.[4–7] The adaptive changes of the autonomic nervous system in heart failure have been regarded as compensatory—that is, beneficial mechanisms to maintain adequate central blood pressure.[8] However, sympathetic stimulation and vagal withdrawal not only induce inotropic and chronotropic effects but also increase impedance for the already impaired pump function of the left ventricle. Consequently, in certain circumstances the changes of autonomic tone might improve cardiac performance, but under other conditions the resulting haemodynamic effect may be deleterious.

We investigated the effects of instantaneous alterations in sympathetic and parasympathetic tone on cardiac performance in patients with either mild (New York Heart Association class 2) or more advanced stages of heart failure (New York Heart Association class 3).

Patients and methods

PATIENTS

We studied thirteen men and one woman (mean (SD) age 54 (3) years and range from 25 to 73 years) with heart failure and sinus rhythm. Five patients had coronary artery disease and nine had primary dilated cardiomyopathy. The diagnosis was confirmed in all patients by right and left heart catheterisation and by selective coronary angiography. All patients were treated with diuretics and 10 were being treated with digitalis; one patient was also given quinidine and another theophylline. All patients gave informed consent to the protocol, which was approved by the ethics committee of the German National Research Foundation, Herzfunktion und Ihre Regulation, SFB 320.

HAEMODYNAMIC MEASUREMENTS

We performed right heart catheterisation using a Swan-Ganz catheter in patients in the postabsorptive state. Cardiac output was measured by thermodilution at baseline in triplicate and once during each period of baroreceptor stimulation. Pulmonary artery and right atrial pressures were recorded. Arterial cannulas were inserted into the radial artery of six patients. The mean of three measurements by the cuff technique was taken as arterial pressure in the remaining patients. The following variables were calculated by standard formula: cardiac index, stroke volume index, mean blood pressure, total peripheral resistance.

Plasma concentrations of catecholamines were measured by the radioenzymatic method of Da Prada and Zürcher.[9] Plasma renin activity and plasma vasopressin were measured by radioimmunoassays.[10 11]

EVALUATION OF THE CAROTID SINUS BAROREFLEX

Carotid sinus baroreflexes were studied by means of the negative pressure technique described by Eckberg *et al*.[12] An airtight chamber was fastened around the neck and painless negative pressure was generated within 0·1 seconds. Steady state conditions were reached within 30 seconds.[13–16] The negative pressure is linearly transmitted to the carotid sinus and selectively stimulates the carotid sinus baroreceptors, causing an immediate decrease of heart rate, and a delayed fall of arterial pressure.[12–16]

STUDY DESIGN

All patients were studied in the supine position. After 30 minutes of rest the baseline haemodynamic data were obtained and blood was drawn for the measurement of plasma concentrations of catecholamines and vasopressin and plasma renin activity. Then a negative pressure of 40 mm Hg was applied to the neck chamber. During the last 20 seconds of negative pressure—that is, between the 30th and 60th second of suction—the haemodynamic data were obtained. Negative pressure was applied twice to the neck of each patient and the mean of the haemodynamic data obtained during the two intervention periods was used for calculations.

The patients were divided into two groups according to a combination of their New York Heart Association class and plasma noradrenaline concentrations at rest. Patients with severe heart failure (New York Heart Association class 3) and simultaneously increased plasma noradrenaline concentrations at rest (> 1·48 nmol/l) were allocated to group A whereas patients with mild heart failure (New York Heart Association class 2) or patients in New York Heart Association class 3 and normal concentrations of plasma noradrenaline at rest (< 1·48 nmol/l) were allocated to group B. Plasma catecholamine concentrations that were more than 2 SD above the mean of a group with normal left ventricular function[7] were regarded as raised. Both groups were similar in age. Four patients in group A and five patients in group B had dilated cardiomyopathy. The other patients had ischaemic cardiomyopathy.

Table 1 Comparison of haemodynamic data at baseline in patients with severe (group A) and moderate (group B) heart failure

	Group A	*Group B*	*p*
Mean blood pressure (mm Hg)	87 (4)	95 (5)	NS
Heart rate (beats/min)	98 (11)	82 (4)	NS
Cardiac index (l/min per m^2)	2·4 (0·2)	3·2 (0·3)	NS
Stroke volume index (ml/m^2)	26 (2)	39 (3)	0·02
Systolic pulmonary artery pressure (mm Hg)	63 (3)	34 (4)	0·001
Diastolic pulmonary artery pressure (mm Hg)	30 (4)	16 (3)	0·01
Mean right atrial pressure (mm Hg)	11 (2)	6 (1)	0·08
Total peripheral vascular resistance (dyn s cm^5)	1362 (134)	1236 (108)	NS

Table 2 Changes of haemodynamic variables during baroreceptor stimulation in patients with severe (group A) and moderate (group B) heart failure

	Group A	*Group B*	*p (between groups)*
Heart rate (beats/min)	−3 (3)	−7 (2)**	NS
Cardiac index (l/min per m^2)	0·8 (0·2)**	−0·3 (0·1)*	0·001
Stroke volume index (ml/m^2)	9 (2)**	0 (1)	0·01
Systolic pulmonary artery pressure (mm Hg)	−10 (5)	−4 (2)	NS
Diastolic pulmonary artery pressure (mm Hg)	−3 (3)	−1 (2)	NS
Mean right atrial pressure (mm Hg)	0 (1)	2 (1)	NS

*p < 0·005, **p < 0·01 for changes compared with baseline values.

STATISTICAL ANALYSIS

Results are given as mean (SEM). The significance of differences was calculated by the *t* test or the signed rank test on paired data and the *t* test or the Mann-Whitney U test on unpaired data. A p value of < 0·05 was regarded as significant.

Results

All patients in group A but only two patients in group B had severe heart failure (New York Heart Association class 3). The other patients were in the New York Heart Association class 2. The New York class of group B (2·2 (0·2)) was lower than that in group A. By definition the mean plasma concentration of noradrenaline was much higher in group A than in group B (2·99 (0·86) nmol/l *v* 0·85 (0·24) nmol/l).

Table 1 shows the baseline haemodynamic data of both groups. In group A pulmonary artery pressures were significantly higher and stroke volume index was significantly lower than in group B. Mean arterial pressure and heart rate did not differ significantly in the two groups.

Plasma renin activity in group B (4·0 (1·2) ng angiotensin I/ml h) was significantly lower than in group A (7·8 (1·0 ng angiotensin I/ml h) (p < 0·05). Plasma concentrations of vasopressin (3·3 (0·9) pmol/l in group A versus 3·2 (0·7) pmol/l in group B) and plasma adrenaline (398·43 (131·00) *v* 278·36 (98·24) pmol/l in group B) were not significantly different in the two groups.

Table 2 shows the haemodynamic responses to baroreceptor stimulation. Pulmonary artery and right atrial pressures did not change significantly in either group. The tendency for heart rate to fall during baroreceptor stimulation was similar in the two groups. All patients in group A had an increase of cardiac output during baroreceptor stimulation (+ 1·5 (0·3) l/min, p < 0·05) whereas in the nine patients in group B cardiac output decreased or remained unchanged (−0·6 (0·2) l/min, p < 0·01). The increase of cardiac output during baroreceptor stimulation in group A was caused by an increase in stroke volume (fig 1, table 2). In group B mean heart rate decreased slightly and because stroke volume did not change cardiac output fell (fig 2, table 2).

The radial artery pressure was measured in three patients in each group during stimulation of the carotid sinus baroreceptors. Mean arterial pressure fell in five patients and remained unchanged in one patient in group B (92 (5) *v* 77 (4) mm Hg; p < 0·05). The number of patients was too small for the changes of blood pressure in each group to achieve statistical significance (table 3). In the three patients with severe heart failure (group A) systemic vascular resistance fell significantly (p < 0·05) whereas the systemic vascular resistance was not altered by baroreceptor stimulation in patients in group B (table 3).

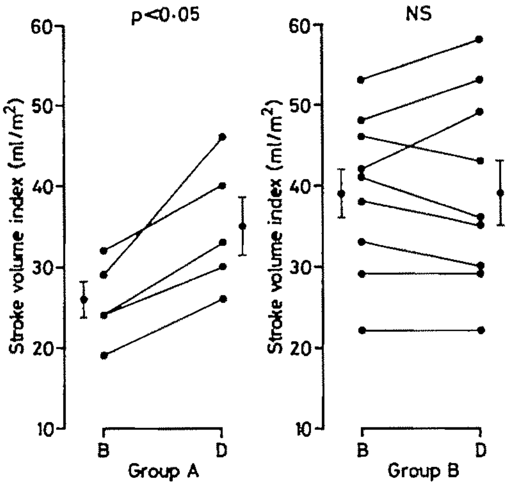

Figure 1 Stroke volume index before (B) and during (C) carotid sinus baroreceptor stimulation in patients with severe (group A) and less severe heart failure (group B).

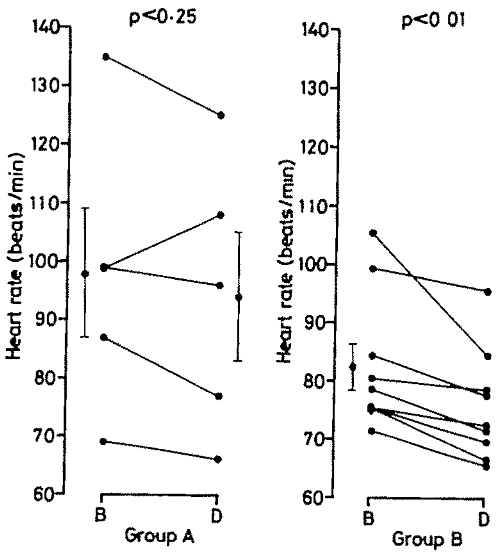

Figure 2 Heart rate before (B) and during (D) stimulation of the carotid sinus baroreceptors.

Discussion

Congestive heart failure is associated with increased sympathetic drive to the heart and blood vessels.[1 2 17] In mild heart failure the increased sympathetic activity is considered to be compensatory to preserve cardiac output. In severe heart failure, however, excessive sympathetic tone can lead to a further deterioration of cardiac function.[18] Physiological withdrawal of sympathetic tone could therefore unmask the effects of sympathetic overactivity. Stimulation of carotid sinus baroreceptors results in a physiological and almost instantaneous reflex withdrawal of sympathetic efferent activity and an increase of vagal efferent tone.[3 12–16] This stimulus was therefore used to assess the haemodynamic changes caused by the alterations of autonomic tone.

The most interesting finding of this study was the instantaneous increase in cardiac output and stroke volume index in patients with severe heart failure (group A), indicating improved cardiac performance when the carotid sinus baroreceptors were stimulated by negative pressure.

The degree of carotid sinus baroreceptor stimulation must have been sufficient to alter the autonomic nervous efferent activity because the arterial pressure decreased significantly in the six patients in whom intra-arterial pressure was monitored. In addition, in patients with mild to moderate heart failure the same degree of baroreceptor stimulation induced a 10 mm Hg fall in blood pressure.[19] Moreover, in normal subjects the same stimulus led to reflex changes of cardiac output, blood pressure, and forearm vascular resistance.[20–25] The hypotensive response after electrical stimulation of the carotid sinus nerves in man is not affected by atropine and therefore must be the result of a reduction in sympathetic vasoconstrictor tone and/or cardiac sympathetic activity.[26] The decrease of heart rate in all patients in group B and in four patients in group A was further indirect evidence that the autonomic tone was altered by the degree of negative pressure that we applied. The activities of the renin-angiotensin or vasopressin system or alterations of body fluid volumes do not change during such short periods of baroreceptor stimulation, and therefore could not have affected the haemodynamic response. Because all cardiovascular reflex changes mediated by arterial baroreceptors are achieved by an integrated response of the autonomic nervous system we concluded that sympathetic tone was reduced and that vagal tone was simultaneously increased during this degree of baroreceptor stimulation.[16]

Table 3 Intra-arterial pressure during baroreceptor stimulation in three patients in group A and three patients in group B

	Group A		*Group B*	
	Before	*During*	*Before*	*During*
Mean blood pressure (mm Hg)	88 (6)	72 (6)	97 (8)	84 (1)
Heart rate (beats/min)	95 (4)	94 (9)	76 (1)	69 (1)*
Cardiac index (l/min per m²)	2·7 (0·2)	3·7 (0·3)*	3·2 (0·2)	2·6 (0·1)
Stroke volume index (ml/m²)	28 (2)	40 (4)*	42 (2)	38 (3)*
Mean right atrial pressure (mm Hg)	10 (3)	9 (4)	7 (1)	5 (1)
Total peripheral vascular resistance (dyn s cm^{-5})	1245 (79)	729 (71)*	1141 (109)	1233 (55)

Significance of differences with the baseline values *$p < 0.005$.

All patients in group A had heart failure in the New York Heart Association class 3, high concentrations of plasma noradrenaline, and high renin activity. Left ventricular filling pressure was higher and stroke volume was lower than in group B. Heart rate tended to be higher in patients in group A. Therefore, patients in group A had more severe heart failure with a greater degree of sympathetic stimulation than patients in group B.

The changes in stroke volume during baroreceptor stimulation of the carotid sinus in group A could be the result of alterations of preload, afterload, and/or inotropic state. Diastolic pulmonary artery pressure (a measure of left ventricular filling pressure) was unchanged in group A during baroreceptor stimulation. The increase of stroke volume in group A could therefore not be explained by an altered preload. Consequently, the increase of stroke volume must have been produced by alterations in the inotropic state or afterload or both.

The substantial decrease of total peripheral vascular resistance during baroreceptor stimulation suggests that the stroke volume was increased by a large decrease in left ventricular afterload. The decrease in afterload was caused by a reduction in the sympathetic vasoconstrictor tone, a reflex response that was reported in animals and humans.[12–16 19–26] A simultaneous increase in inotropic state seems less likely. The beneficial effect of a nearly immediate reduction in sympathetic tone on stroke volume provides evidence that sympathetic overactivity may be detrimental in human heart failure; reflex sympathetic withdrawal improved the patient's condition. This mechanism might also explain the poor prognosis in patients with high degrees of sympathetic activity.[2]

The reflex decrease of heart rate during stimulation of the carotid sinus baroreceptors in patients with heart failure was abolished by atropine and therefore must depend on an increase in vagal efferent tone.[3 16] The same mechanism may be assumed in group A because heart rate decreased slightly in four out of five patients.

In contrast, the patients with only mild or moderate degrees of left ventricular dysfunction (group B) showed haemodynamic responses to stimulation of the carotid sinus baroreceptors that resembled those in healthy subjects. Direct stimulation of the carotid sinus nerve and stimulation of the carotid sinus baroreceptors by negative pressure caused a slight decrease in heart rate in healthy volunteers.[20–25] Cardiac output was either unchanged[23] or decreased[20 24] during 40 mm Hg of negative pressure. The same degree of baroreceptor stimulation in group B caused a fall in cardiac output owing to a reduction in heart rate. The design of our study meant that we were unable to determine why stroke volume was unchanged. The unaltered systemic vascular resistance at a presumably lower blood pressure suggests that withdrawal of sympathetic vasoconstrictor tone caused a decrease in left ventricular afterload. Because preload did not change during baroreceptor stimulation the likely explanation was that a reflex withdrawal of the inotropic sympathetic support to the heart was balanced by a reduction of afterload, resulting in an unchanged stroke volume. The degree of autonomic activity in these patients may therefore be regarded as a compensatory response to preserve cardiac output.

The results of this study show that patients with severe heart failure may benefit from withdrawal of their intrinsic autonomic tone. Drugs that reduce the sympathetic tone may lead to haemodynamic improvement in such patients.

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Time of occurrence, duration, and ventricular rate of paroxysmal atrial fibrillation: the effect of digoxin

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Abstract

One hundred and thirty nine episodes of atrial fibrillation were identified from Holter recordings in 72 patients with paroxysmal atrial fibrillation. Paroxysms occurred more often by day than by night, suggesting that attacks are more closely associated with sympathetic than with vagal activity. In 41 patients who were not taking digoxin there were 79 episodes, and in 31 patients who were taking digoxin there were 60 episodes. Significantly more of the episodes that lasted for 30 minutes or more occurred in patients taking digoxin (13/17); the relative risk of a prolonged paroxysm associated with taking digoxin was 4·3 (95% confidence intervals 1·6–11·9). The mean (SD) ventricular rate at the onset of the paroxysms was not significantly different in those taking digoxin (140 (25) beats/min) and in those who were not (134 (22) beats/min).

In paroxysmal atrial fibrillation, pretreatment with digoxin does not seem to reduce the frequency of paroxysms, or the ventricular rate when paroxysms occur, but it is associated with longer attacks.

In paroxysmal atrial fibrillation some patients may experience distressing symptoms at the onset of a paroxysm, symptoms that are related to the tachycardia usually present when atrial fibrillation starts. Digoxin is generally effective in established atrial fibrillation in reducing the ventricular rate of patients at rest. It achieves this effect indirectly by slowing conduction through the atrioventricular node by increasing vagal tone. Digoxin is also sometimes used in paroxysmal atrial fibrillation in the hope that it will reduce the ventricular rate when paroxysms start.[1 2] However, in some patients with paroxysmal atrial fibrillation, paroxysms are more likely to occur at times of increased vagal activity, such as during sleep,[3] so digoxin, with its vagotonic effect, may increase the frequency of attacks.[4] Moreover, by its action in reducing the atrial refractory period digoxin may make reversion to sinus rhythm less likely. Whether pre-treatment with digoxin is effective in reducing the ventricular rate in paroxysmal atrial fibrillation, or whether digoxin causes attacks to be more prolonged is not known.

Since autonomic tone affects the likelihood of the occurrence and perpetuation of atrial fibrillation, variation of the rate of occurrence of attacks would be expected in parallel with the known diurnal variation of autonomic activity.[5] In this study we noted the times of day that episodes of atrial fibrillation occurred. We also compared the ventricular rates at the onset of paroxysms, and noted the number of prolonged paroxysms, in patients with and without digoxin therapy.

Patients and methods

We selected Holter recordings showing paroxysmal atrial fibrillation in 72 consecutive patients who were being investigated for clinical reasons. All patients were in sinus rhythm at the start and end of the recordings, which lasted for 48 hours. For the purposes of this study paroxysmal atrial fibrillation was defined as the occurrence of at least five beats of supraventricular origin, with a totally irregular ventricular response, with no visible P or flutter waves, the arrhythmia lasting less than 24 hours. Seventy two patients (32 men and 40 women; mean age 72 (range 34–93) had arrhythmias which fulfilled these criteria. Associated diagnoses were as follows: none 45, ischaemic heart disease 12, sinoatrial disease 11, valvar heart disease two, hypertension two. Thirty one patients were taking digoxin, 11 were taking a β adrenergic blocker (five with digoxin), and nine were taking a calcium channel blocker (three with digoxin). We calculated the serum concentration of digoxin from the serum creatinine concentration and the body weight, using a nomogram based on the pharmacokinetics of digoxin.[6] The calculated serum digoxin concentration was 0 μg/l in 41, up to 1 μg/l in 11, and over 1 μg/l in 20 patients.

The time of onset of each paroxysm was noted together with the ventricular rate, calculated from the first 5–10 beats of each paroxysm. In the case of prolonged bouts of atrial fibrillation lasting 30 minutes or more, the duration of the attack and the ventricular rate immediately before it ended were noted.

Results

TIME OF DAY OF PAROXYSMS (fig 1)

There were 139 paroxysms recorded in 72 patients, an average of 1·9 episodes during a two day recording (range one to seven). Of the total, 26 (19%) paroxysms occurred between the hours of 2200 and 0600, 56 (40%) between 0600 and 1400, and 57 (41%) between 1400 and

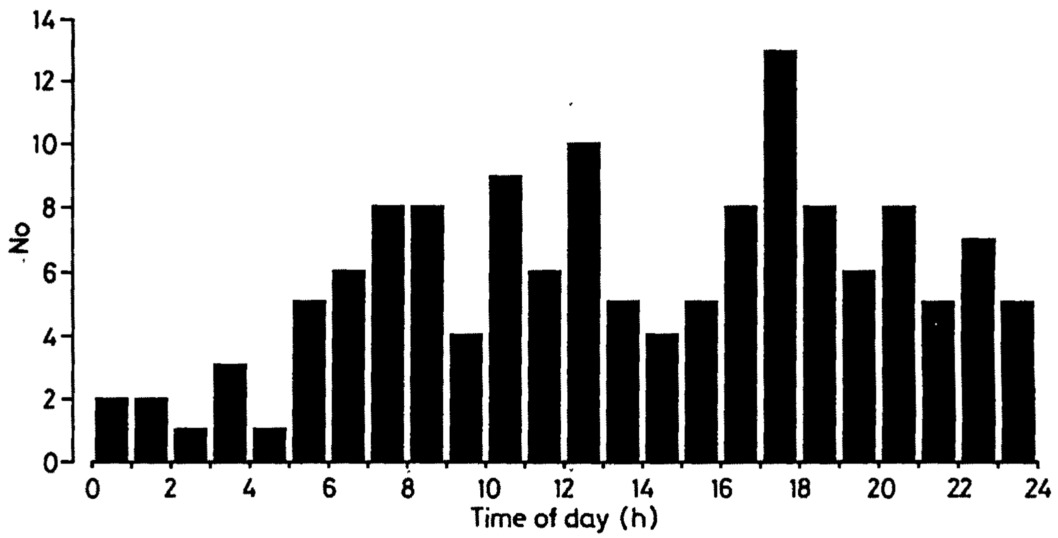

Figure 1 Numbers of paroxysms of atrial fibrillation throughout the day and night.

2200. This distribution of paroxysms throughout the day was non-random ($\chi^2 = 13\cdot4$, df = 2, $p < 0\cdot005$).

There were 17 prolonged episodes of atrial fibrillation lasting 30 or more minutes (range 30–1100 minutes). Their temporal distribution did not differ from that which could have occurred by chance ($\chi^2 = 0\cdot82$, df = 2, NS).

PROLONGED EPISODES AND DIGOXIN TREATMENT

Thirteen of 17 patients with prolonged episodes of atrial fibrillation were taking digoxin, compared with 18 out of 55 patients who did not have prolonged episodes ($\chi^2 = 8\cdot4$ with Yates's correction, $p < 0\cdot01$). The relative risk of prolonged episodes of atrial fibrillation associated with digoxin treatment was 4·3 (95% confidence interval 1·6–11·9).

VENTRICULAR RATES DURING PAROXYSMAL ATRIAL FIBRILLATION

The mean (SD) ventricular rate at the start of all paroxysms of atrial fibrillation was 136 (23·6) beats/min. The mean ventricular rate was not significantly different in patients taking or not taking digoxin (140 (25·3) *v* 134 (22·2) beats/min, NS). Figure 2 shows the relation of the mean ventricular rates to calculated serum digoxin concentrations.

The mean ventricular rate at the start of prolonged episodes of atrial fibrillation was 140 (33·9) beats/min, and this was similar to that at the start of short bursts. The ventricular rate at the start of prolonged episodes was not significantly different from that immediately before spontaneous termination, when it was 138 (27·3) beats/min.

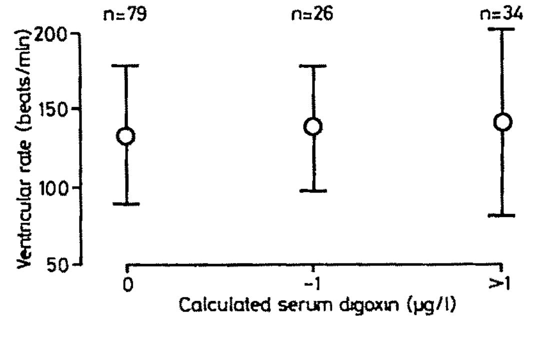

Figure 2 Mean (95% confidence intervals) ventricular rates for patients with three calculated serum digoxin concentrations.

EFFECTS OF OTHER TREATMENT

The number and time of day of paroxysms, the number of prolonged paroxysms, and the ventricular rates were not significantly different in the small number of patients taking β adrenergic blockers or calcium channel blockers compared with patients not taking these drugs.

Discussion

Paroxysmal atrial fibrillation is a difficult disorder to investigate because of its essentially intermittent nature. In this study, where patients were selected by virtue of the chance recording of episodes of atrial fibrillation, the incidence of attacks was slightly less than one per day, of which 88% lasted less than half an hour. Any prospective study of paroxysmal atrial fibrillation is therefore severely hampered by the difficulty of documenting the occurrence of infrequent and usually brief episodes.[7] Our study was not a randomised prospective trial, and the way in which patients were selected may have resulted in bias. Nevertheless, our observations add to knowledge in this difficult area.

Atrial dilatation, a shortened refractory period, reduced conduction velocity, and nonuniform repolarisation increase the likelihood of the induction of atrial fibrillation,[8] which may be triggered by an extrasystole arising from an irritable, ectopic focus.[9] These conditions are found in a wide variety of physiological, pathological, and experimental states. Thus, cholinergic drugs applied directly to the atrium,[10] or acetylcholine released by vagal stimulation[11 12] shorten the atrial refractory period and may lead to atrial fibrillation, especially if there is atrial distension with fibrosis or other pathological features.[13] Sympathetic stimulation, which may coexist with vagal activity,[14] may also bring about the same end result by increasing cardiac excitability and hence the occurrence of extrasystoles. Precipitation of atrial fibrillation under clinical conditions of sympathetic or parasympathetic predominance has been described.[4]

Digoxin enhances vagal tone, increasing the refractory period of the atrioventricular node. In established atrial fibrillation this property of digoxin is used to increase the degree of atrioventricular block and so reduce ventricular rate. It is most effective in this when vagal tone is already high, and relatively ineffective when vagal tone is low. Thus, although ventricular rate at rest may be controlled by digoxin, during exercise, when vagal tone is withdrawn and sympathetic activity predominates, ventricular rate may be regarded as excessive.[15]

Digoxin also shortens the refractory period of atrial muscle, rendering the atrium more susceptible to fibrillation and increasing the rate of fibrillation should it occur. The result of its use in atrial fibrillation is therefore a compromise between increased fibrillation rate and reduced atrioventricular conduction, with the beneficial effect of the reduced conduction generally predominating.

In the patients selected for this study, paroxysms of atrial fibrillation were twice as likely to occur by day as by night, suggesting that attacks were more closely associated with sympathetic activity than with vagal activity. Attacks were as frequent in patients taking digoxin as in those who were not. Mean ventricular rates during attacks were high and no different in patients taking or not taking digoxin. This lack of benefit from digoxin may have resulted from the conditions of low vagal tone and sympathetic predominance under which most of the paroxysms may be presumed to have arisen.

While there is no evidence of reduction of ventricular rate during paroxysmal atrial fibrillation, there is evidence that the use of digoxin resulted in longer attacks, a result consistent with its action in reducing the atrial refractory period.

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Study of serum C-reactive protein concentration in cardiac failure

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Abstract

The serum concentration of C-reactive protein was prospectively assessed in 37 patients with various degrees of heart failure. The serum concentration of C-reactive protein was higher than normal in 26 (70%) patients. The concentration was directly related to the severity of heart failure and the stage of decompensation. Hepatic cell damage is the most likely stimulus to cytokine production and hence release of C-reactive protein in heart failure. Heart failure is an additional cause of raised serum concentration of C-reactive protein but the pathological importance of this feature is not yet known.

C-reactive protein is synthesised in the liver and is an acute phase reactive protein. Its concentration in serum rises rapidly in patients in response to tissue injury, infection, or inflammation.[1] When the stimulus resolves, for example, with effective antimicrobial treatment, the concentration falls rapidly.[2] Measurements of C-reactive protein were useful in diagnosing and assessing the extent of damage in myocardial infarction.[3-5] More recently it has been proposed as a marker of successful thrombolysis and early reperfusion in myocardial infarction.[6] It has provided a complementary diagnostic test in infective endocarditis and has been used as an index of response to treatment in this condition.[7] We noticed that patients who had evidence of heart failure in the absence of acute myocardial infarction, systemic infection, or inflammatory disease had raised serum concentrations of C-reactive protein. The acute phase protein response has not been studied in heart failure. We prospectively studied serum concentrations of C-reactive protein in patients with varying degrees of heart failure.

Patients and methods

PATIENTS

We studied 37 patients admitted to hospital for investigation and treatment of cardiac failure (table 1). Heart failure was caused by ischaemic heart disease in 20, valve disease in 10, idiopathic dilated cardiomyopathy in six, and systemic hypertension in one. We also measured the serum concentrations of C-reactive protein in 15 control patients admitted for routine coronary arteriography with no clinical evidence or history of heart failure and normal left and right ventricular function. Venous blood samples were obtained from patients on admission and every 24–48 hours during their hospital stay. The control group were sampled before and 24 hours after coronary arteriography.

DEFINITIONS

The diagnosis of cardiac failure was based on the following:

(*a*) Left heart failure—sinus tachycardia > 90/min with a third heart sound and clinical or radiological evidence of a raised pulmonary venous pressure.

(*b*) Right heart failure—raised jugular venous pressure with or without congestive hepatomegaly and with or without peripheral oedema.

This was supported by objective evidence of left or right ventricular dysfunction with

Table 1 Clinical details and peak concentrations of serum C-reactive protein in 37 patients in heart failure

Patient no	*Age (yr)*	*Sex*	*Diagnosis*	*Cause*	*Stage*	*Severity*	*LVEF (%)*	*Peak CRP (mg/ml)*
1	56	M	L+RHF	IHD	Acute	Severe	15	51
2	57	F	L+RHF	IHD	Acute	Severe	17	72
3	63	M	L+RHF	IHD	Acute	Severe	12	90
4	69	F	L+RHF	DCM	Acute	Severe	20	16
5	63	M	LHF	IHD	Chronic	Severe	15	21
6	68	M	L+RHF	Valve*	Acute	Severe	30	67
7	61	M	LHF	IHD	Acute	Severe	15	71
8	63	M	RHF	Valve	Chronic	Severe	35	19
9	55	F	L+RHF	DCM	Acute	Severe	12	20
10	63	F	RHF	Valve	Chronic	Mild	40	<10
11	55	F	RHF	Valve	Chronic	Mild	35	<10
12	53	M	LHF	IHD	Acute	Severe	20	120
13	52	F	L+RHF	DCM	Acute	Severe	15	47
14	45	M	L+RHF	IHD	Chronic	Moderate	20	87
15	52	F	L+RHF	IHD	Acute	Severe	20	135
16	50	F	L+RHF	Valve	Acute	Severe	30	22
17	62	F	RHF	Valve	Acute	Moderate	33	27
18	61	M	L+RHF	IHD	Acute	Severe	29	<10
19	60	M	LHF	IHD	Chronic	Severe	15	<10
20	63	M	LHF	Hypertension	Chronic	Severe	35	<10
21	58	F	LHF	Valve	Chronic	Moderate	30	16
22	62	M	L+RHF	IHD	Acute	Severe	20	51
23	60	M	LHF	IHD	Chronic	Moderate	24	<10
24	62	M	RHF	Valve	Chronic	Moderate	35	36
25	55	M	L+RHF	IHD	Chronic	Mild	16	29
26	49	M	L+RHF	IHD	Acute	Severe	24	38
27	59	F	L+RHF	Valve	Chronic	Mild	28	<10
28	57	M	RHF	Valve	Chronic	Severe	23	<10
29	63	F	L+RHF	DCM	Acute	Severe	20	40
30	62	M	L+RHF	IHD	Acute	Severe	14	75
31	67	F	L+RHF	DCM	Acute	Severe	19	34
32	63	M	L+RHF	IHD	Acute	Severe	15	83
33	64	F	LHF	IHD	Chronic	Severe	29	15
34	57	M	LHF	IHD	Chronic	Mild	30	<10
35	65	F	LHF	DCM	Acute	Severe	20	<10
36	63	M	L+RHF	IHD	Chronic	Mild	32	20
37	68	F	L+RHF	IHD	Chronic	Mild	28	<10

*Aortic and/or mitral disease
DCM, dilated cardiomyopathy; IHD, ischaemic heart disease, LHF, left heart failure; RHF, right heart failure; LVEF, left ventricular ejection fraction; CRP, C-reactive protein.

Table 2 Classification of degree of cardiac failure

Category	*CXR*	*Mean PCWP (mm Hg)*	*Peripheral perfusion*
Mild	Vascular redistribution	13–17	Normal
Moderate	Interstitial oedema	18–23	Normal
Severe	Alveolar oedema	>23	Reduced

CXR, appearance on chest *x* ray; PCWP, pulmonary capillary wedge pressure.

either echocardiography, radionuclide scanning, or invasive haemodynamic measurement of pulmonary capillary wedge pressure. Patients were classed as having mild, moderate, or severe heart failure on the basis of peripheral perfusion and radiologically estimated or directly measured pulmonary capillary wedge pressure (table 2). Poor peripheral perfusion was based on finding two or more of the following criteria: (*a*) skin vasoconstriction, (*b*) hypotension (systolic blood pressure <90 mm Hg by cuff method), and (*c*) raised blood urea in the absence of any other identifiable cause. A few patients fitted into more than one class of severity and were placed in the highest category attained on the basis of any criterion. Heart failure was defined as acute if the onset or decompensation has occurred within one month and as chronic if it had occurred more than one month before presentation. We did not distinguish between acute or acute on chronic heart failure in our analysis.

EXCLUSION CRITERIA

We excluded patients with clinical or laboratory evidence of systemic infection or inflammatory or neoplastic disease. We monitored cardiac enzymes and electrocardiograms to exclude any patient who had had a recent (<7 days) myocardial infarction.

MEASUREMENT OF C-REACTIVE PROTEIN

We measured serum concentrations of C-reactive protein by fluorescence polarimetry. The intra-assay coefficient of variation was <5% and a concentration of <10 µg/ml was regarded as normal.[8]

STATISTICAL ANALYSIS

Groups were compared by the unpaired *t* test, and a p value <0·05 was regarded as significant.

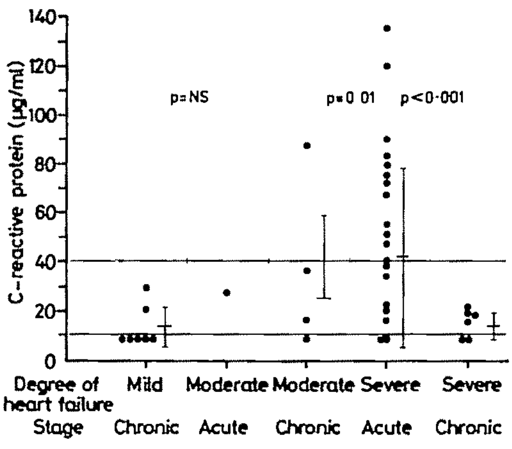

Figure 1 Comparison between stage and degree of heart failure and serum concentration of C-reactive protein.

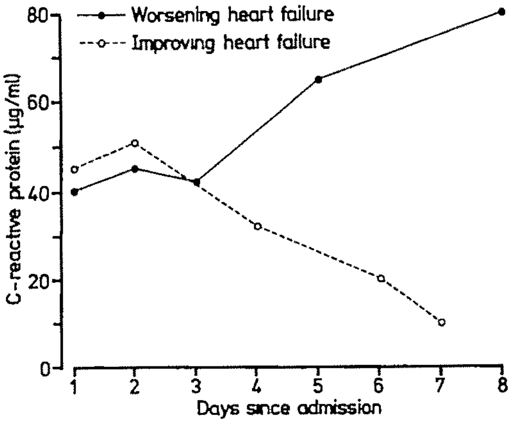

Figure 2 Serial concentrations of serum C-reactive protein from two patients with left ventricular failure who responded differently to treatment.

Results

Twenty six (70%) of the 37 patients had a raised serum concentration of C-reactive protein (table 1). None of the 15 control patients had a raised serum concentration. In 14 (38%) patients it was slightly raised (10–40 µg/ml) and in 12 patients (32%) it was considerably raised (>40 µg/ml). Figure 1 shows the relation between the degree of heart failure and the serum concentration of C-reactive protein. All but one of the 12 patients with a C-reactive protein concentration >40 µg/ml had severe heart failure and acute rather than chronic heart failure. Six patients had isolated right ventricular failure caused by valve disease or fixed pulmonary hypertension and all had serum concentrations of C-reactive protein <40 µg/ml. When acute cardiac failure was stabilised or improved with treatment the serum concentration of C-reactive protein gradually returned to normal values. Conversely in patients who deteriorated the serum concentrations of C-reactive protein tended to remain high (fig 2).

Serum concentrations of aspartate and alanine transaminases were raised in 33% and 23% of the patients respectively. There was no direct correlation between the serum concentration of C-reactive protein and transaminase concentrations, which were more commonly raised in acute severe cardiac failure. The concentration of serum γ-glutamyl transpeptidase too was more often (40%) raised in these patients but once again there was no close correlation with the serum concentration of C-reactive protein.

Discussion

We found that serum concentrations of C-reactive protein were higher than normal in 70% of patients with cardiac failure although in about half the increase was quite small (<40 µg/ml). There was a significant difference between the serum concentrations of C-reactive protein in those with acute and chronic severe heart failure (fig 1). All but one patient with a considerably increased serum concentration of C-reactive protein (>40 µg/ml) had severe cardiac failure. The tendency for concentrations of C-reactive protein to fall with successful treatment (fig 2) also suggests that the severity of cardiac failure directly influences serum concentrations of C-reactive protein. In keeping with these findings de Beer *et al* noted that in eight patients whose recovery after a myocardial infarction was complicated by cardiac insufficiency or low output state, the serum concentration of C-reactive protein did not return to normal as it did in uncomplicated myocardial infarction.[4] Subgroup analysis of patients with predominantly forward or backward heart failure showed no significant difference in the serum concentrations of C-reactive protein.

C-reactive protein is synthesised by hepatocytes and normally only a trace is present in the plasma. It is part of the protein response in the acute phase to tissue injury along with other plasma proteins such as antitrypsin, caeruloplasmin, and fibrinogen. The rate of synthesis and secretion of C-reactive protein increases within hours of acute injury or the onset of inflammation.[9,10] This is probably under the influence of several hormonal mediators called cytokines—for example IL6 or hepatocyte stimulating factor. We think hepatic necrosis is the most likely site of tissue damage that leads to macrophage activation, cytokine production, and release of C-reactive protein in patients with heart failure. Hepatic centrilobular necrosis has been described in isolated left and right heart failure and congestive heart failure as a result of reduced cardiac output, hypoperfusion, hypoxia, and venous congestion.[11–13] This necrosis is often accompanied by alterations in other indices of liver damage or function particularly hepatic release of transaminase.[11,13,14] In this present study serum concentrations of alanine and aspartate transaminase were raised in about a third of patients and the concentration of γ-glutamyl transpeptidase was more often raised. The synthesis and release of C-reactive protein is perhaps a more sensitive indicator of hepatic damage in this situation than either the concentrations of transaminase or transpeptidase. Alternatively, there may be additional sites of tissue damage in cardiac failure, for example kidney, brain, or skeletal muscle. Other possible causes of release of C-reactive protein in this clinical setting include occult infection or pulmonary thromboembolism. There was no clinical evidence of these complications and all patients with a significant fever—that is >37·0°C on two occasions—or clinical evidence of any infection were excluded from the study even if blood, secretion, or tissue cultures were negative. Ventilation-perfusion lung scans were performed in nine patients and all were negative. In addition, 15 patients were well controlled on long term treatment with anticoagulants.

The serum concentration of C-reactive protein provides a simple screening test for the presence of organic disease and is widely used. Because an increase in C-reactive protein is a non-specific response to tissue injury it must be interpreted in the light of clinical information. This study shows a further condition in which the serum concentration of C-reactive protein is raised. It is important to be aware of this phenomenon when measurements of C-reactive protein are interpreted—for example in patients with leaking prosthetic cardiac valves, heart failure, and suspected infective endocarditis. It also raises the question whether acute phase reactive proteins or cytokines are involved in the pathogenesis of cardiac failure or are simply markers of tissue injury.

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Reduction of factor VII coagulant activity (VIIC), a risk factor for ischaemic heart disease, by fixed dose warfarin: a double blind crossover study

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Abstract

An increase in factor VII coagulant activity is known to be an important risk factor for ischaemic heart disease. Four hundred and eight healthy male Post Office workers were screened in an occupational survey. Sixty eight (16·5%) of these had values of factor VII coagulant activity > 1·0 SD above the age related mean. A randomised double-blind crossover study was undertaken to investigate the effect of a fixed daily minidose of warfarin (1 mg) on the high activities of factor VII in these men. Forty two agreed to enter the study and 40 completed it. Their mean factor VII coagulant activity before warfarin treatment was 135·9%. Treatment with a fixed minidose of warfarin significantly reduced factor VII coagulant activity to 124·6%; there was no change on placebo. The prothrombin time was also significantly prolonged on active treatment although all the results remained within the normal range.

These findings suggested a fixed minidose warfarin regime might be useful in the primary prevention of ischaemic heart disease by reducing high activities of factor VII.

High activities of the procoagulant clotting zymogen factor VIIC were shown to be an important risk factor for ischaemic heart disease and to be of even greater significance than cholesterol in the first five years after screening.[1,2] Warfarin given in conventional adjusted doses according to the response of prothrombin time reduces the activity of factor VIIC. Bern *et al*, however, recently showed that much less intense treatment with a small fixed dose of warfarin (2 mg daily) prevented blocking of central venous catheters in patients with malignant disease.[3] Subsequently, we showed that an even smaller fixed dose (1 mg warfarin daily) significantly reduced the incidence of postoperative deep vein thrombosis.[4]

The possibility that 1 mg warfarin daily might also reduce raised factor VII coagulant activity in healthy individuals was considered in the present study. We assessed the effects of this regimen in a randomised double blind crossover study in men with high factor VII coagulant activity.

Patients and methods

DESIGN OF STUDY

Four hundred and eight healthy male Post Office workers (age range 18–65 years) took part in an occupational screening programme during which their prothrombin time and factor VII coagulant activity were measured. Factor VII coagulant activity increases with age.[5,6] Forty two of the 68 men with high activity (> 1 SD above the age related mean) agreed to participate by written informed consent.

In this selected group a repeat assay was performed during the three week period before the start to establish a pretreatment baseline. The 42 men were then allocated by random numbers to receive either warfarin (1 mg/day) or matched placebo for an initial twelve weeks. A further blood sample was then taken and the treatment regimens were crossed over for the second twelve weeks. The tests were then repeated.

LABORATORY METHODS

Fasting venous blood samples were taken between 0800 and 0900 h on each occasion by means of a 19 gauge butterfly and plastic syringes. The blood (9 volumes) was anticoagulated with 3·2% trisodium citrate (1 volume) and centrifuged at 2000 *g* for 15 minutes. Factor VII coagulant activity and prothrombin times were estimated in duplicate within one hour of sample collection. All assays were performed blind.

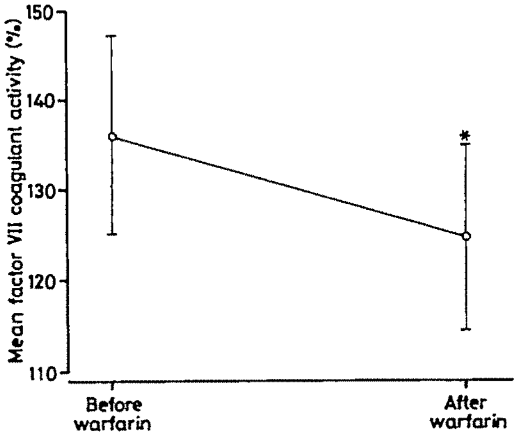
Factor VII coagulant activity assay

This was estimated in a one stage method with factor VII-deficient beagle plasma.[7] A standard curve was obtained from pooled plasma prepared from 20 blood donor volunteers. The participants' results were expressed as a percentage of the value from the normal pool. Inter assay variation was assessed by the International Standard for factor VII coagulant activity (National Institute for Biological Standards and Control, London). The same batches of reagents were used throughout the study.

Prothrombin time

Prothrombin time was measured with Manchester Reagent thromboplastin. Inter batch variation was excluded by the use of calibrated lyophilised normal reference plasma samples prepared at the UK Reference Laboratory for Anticoagulant Reagents and Control.

*Figure 1 Factor VII coagulant activity (mean (2 SE)) before and after 12 weeks on a fixed daily dose of 1 mg warfarin. *Significant fall, $p = 0.03$.*



STATISTICAL ANALYSIS

We used log transformed values of factor VII coagulant activity because their distribution was positively skewed. Differences between and within groups were analysed by a repeated measures analysis of variance.[8] We examined significant differences in detail using the Tukey range test[8] as required. Analysis was performed on an "intention-to-treat" basis.

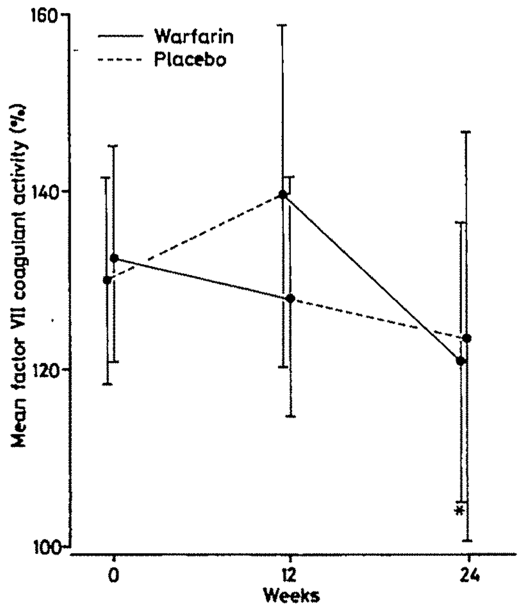
Results

Forty of the 42 men completed the study. Two withdrew for non-medical reasons. The age range was 31–61 years (mean 47·1). Compliance, estimated by counting the returned tablets, was 90% throughout the study in both groups.

When the results of the two groups were combined, fixed minidose warfarin was found to be associated with a significant reduction in factor VII coagulant activity, with a mean fall of 11·3% ($p = 0.03$) from the values immediately before the start of warfarin treatment. There was a fall in mean factor VII coagulant activity from 135·9% before warfarin treatment (95% confidence limits 124·8–147·0%) to 124·6% (114·4–134·8%) after 12 weeks' warfarin treatment (fig 1).

Figure 2 shows the serial changes in factor VII coagulant activity in the two order groups. This showed that the fall in factor VII coagulant activity in the men receiving warfarin first did not achieve statistical significance but in those receiving warfarin second the reduction in factor VII coagulant activity was significant ($p = 0.05$). There was a non-significant increase in factor VII coagulant activity in those receiving placebo first and a non-significant reduction in those receiving placebo after warfarin.

*Figure 2 Factor VII coagulant activity (mean (2 SE)) during treatment with a fixed daily dose of 1 mg warfarin and during treatment with placebo. *Significant difference after warfarin treatment, $p < 0.05$.*



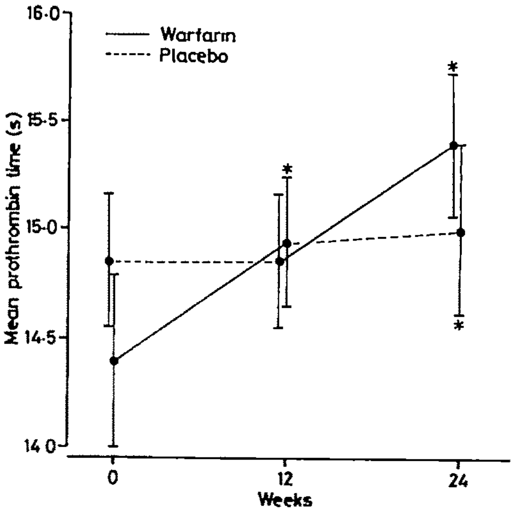


*Figure 3 Prothrombin times (mean (2 SE)) during treatment with a fixed daily dose of 1 mg warfarin and during treatment with placebo. *Significant difference compared with baseline, $p < 0.05$.*

There was a significant difference at baseline ($p < 0.01$) in the prothrombin time between those receiving warfarin first and placebo first, which has been allowed for in the analysis (fig 3). On no occasion was the prothrombin time prolonged outside the normal range (13·5–17·5 s) but both groups showed that the prothrombin time during warfarin treatment was significantly longer than the immediate pretreatment values ($p < 0.05$). In those receiving warfarin first the prolongation of the prothrombin time was maintained at the end of the placebo period. No clinical side effects of treatment were reported.

Discussion

The study showed that a very small fixed dose of warfarin (1 mg daily) significantly reduced factor VII coagulant activity in healthy male Post Office workers with high activities. The fixed daily dose of 1 mg of warfarin that we used is much less than the range of mean adjusted maintenance daily doses (2·45–8·76 mg) reported in an international survey.[9] It is also considerably less than the mean daily doses of 5·8 and 4·9 mg used by Hull and colleagues to prevent recurrent venous thrombosis.[10] In an earlier study we found that the fixed daily dose of 1 mg warfarin significantly reduced the incidence of deep vein thrombosis after major surgery.[4] This suggested that a small reduction in factor VII coagulated activity achieved with this regimen is clinically effective, and might also protect against the subsequent development of ischaemic heart disease. The effects of fixed minidose warfarin have not previously been investigated in individuals predisposed to arterial disease.

The present results suggest that the fixed dose of 1 mg warfarin daily might have beneficial effects on this major risk factor for ischaemic heart disease without disturbance of normal haemostasis. The reduction in factor VII coagulant activity was associated with a parallel prolongation of the prothrombin time, but within the limits of the normal range. The effect on the prothrombin time was more uniform than that on factor VII coagulant activity in the two groups presumably because the prothrombin time unlike the assay for factor VII coagulant activity also reflects depression of additional clotting factors reduced by warfarin—for example factors II and X. The sustained depression of factor VII coagulant activity in the group receiving warfarin first was unexpected and of interest but requires confirmation by further study.

Meade *et al* showed a positive association between factor VII coagulant activity and the subsequent development of ischaemic heart disease.[1,2] This relation seemed even stronger than the well recognised association between raised cholesterol in the subsequent 5 years and the mortality from ischaemic heart disease. Factor VII coagulant activity was high after recent thrombosis[11] and in several states associated with an increased risk of ischaemic heart disease, including increasing age,[5,6] hyperlipidaemia,[12,13] obesity,[14] high fat intake,[15] and diabetes.[16] Raised activity of factor VII coagulant activity was also associated with use of oral contraceptives,[17] pregnancy,[18,19] and the menopause.[20]

The therapeutic range for the treatment of arterial disease, including myocardial infarction, recommended by the British Society for Haematology is an International Normalised Ratio of between 3·0 and 4·5.[21] This represents a minimum prolongation of 30 seconds over the upper limit of the normal range with the Manchester Reagent thromboplastin used to measure the prothrombin time in the present study. The maximum prolongation in any of our subjects was 2·25 s and in no instance did the prothrombin time exceed the upper limit of the normal range.

Oral anticoagulant treatment has been claimed to be effective in secondary prevention of myocardial infarction when given in traditional adjusted doses[22] but no studies have yet been published on the value of oral anticoagulants in the primary prevention of ischaemic heart disease. A large clinical trial is, however, in progress in the United Kingdom to see whether less intense anticoagulation (target International Normalised Ratio 1·5) with an adjusted dose of warfarin is effective.[23]

The epidemiological evidence indicates that raised activity of factor VII is an important risk factor for ischaemic heart disease. It is possible therefore that reduction of high activities by fixed dose warfarin might be beneficial. To investigate this requires a much larger series of high risk subjects with raised factor VII coagulant activity followed for a considerably longer period. Minidose warfarin may have the advantage of not requiring frequent or regular laboratory monitoring, which is an essential prerequisite and limitation of adjusted dosage.

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Phaeochromocytoma and catecholamine induced cardiomyopathy presenting as heart failure

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Abstract

Phaeochromocytoma is rare and usually presents as paroxysmal or sustained hypertension; none the less, it can also cause severe acute pulmonary oedema in normotensive individuals.

Six patients with phaeochromocytoma presenting in Cornwall and West Devon between 1982 and 1986 are described. Five of them died of pulmonary oedema within 24 hours of the onset of symptoms. At necropsy all five had normal sized hearts and in the four hearts examined by histology there was evidence of catecholamine induced heart disease in the form of focal myocardial necrosis. The sixth patient presented with arterial spasms and pulmonary oedema. Surgical removal of the causative tumour was successful in this patient.

The commonest manifestations of phaeochromocytoma are paroxysmal or sustained hypertension with paroxysms of adrenergic stimulation, causing palpitation, headaches, sweating, pallor, tremors, and anxiety.[1] Phaeochromocytomas account for about 0·04% of cases of hypertension,[2] but there is a distinct group of patients with phaeochromocytoma who remain normotensive despite active metabolites being secreted.[3 4] Sometimes high blood pressure may fall back to normal values because of myocardial damage,[5] and normotensive patients who do not have paroxysmal symptoms may be more likely to die as a result of adrenergic heart disease because the diagnosis is not suspected.[6] Although rare, hypotension can occur when β adrenergic stimulation overrides α adrenergic stimulation.[3]

Acute pulmonary oedema is less widely recognised as a feature of phaeochromocytoma. We report six such patients, of whom five presented with acute pulmonary oedema.

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Case reports

PATIENT 1

A 71 year old woman was admitted to hospital as an emergency with acute chest pain and breathlessness. She was tachycardic (heart rate 150 beats/min), tachypnoeic (respiratory rate 36 per min), pyrexial (axillary temperature 40°C), and cyanosed. She was normotensive (blood pressure 130/80 mm Hg) and the jugular venous pressure was not raised. Heart sounds were unremarkable and there were bilateral scattered crepitations. The chest *x* ray showed a slightly enlarged cardiac shadow and pulmonary oedema. The electrocardiogram showed sinus tachycardia, poor R wave progression in the chest leads, and non-specific T wave changes. Full blood count and electrolytes were normal and analysis of arterial blood gases showed Po_2 9·8 kPa, Pco_2 3·2 kPa, and pH 7·2. She deteriorated rapidly and despite resuscitative measures she died within two hours of admission.

At necropsy the heart weighed 285 g (normal 250–400 g) with minimal dilatation of both ventricles. No significant lesions were found in the coronary arteries and histological examination of the heart showed patchy muscle fibre necrosis with phagocytosis. Severe haemorrhagic oedema was found in both lungs, which showed no evidence of acute pulmonary infarction. A tumour 4 cm in diameter was found in the right adrenal gland and histology showed this to be a phaeochromocytoma.

PATIENT 2

A 63 year old woman was admitted with a history of chest pain and breathlessness for two hours. The week before she had presented to the local cottage hospital with malaise, pedal oedema, and non-specific chest discomfort. She had had no other significant problems in the past and had never had hypertension. On admission she was pale with sinus tachycardia of 146 beats/min and blood pressure of 110/70 mm Hg. Jugular venous pressure was 3 cm above the sternal angle and auscultation showed a gallop rhythm. She had widespread crepitations in both lung fields. The electrocardiogram showed no evidence of myocardial infarction or left ventricular hypertrophy and the chest *x* ray was consistent with pulmonary oedema. She was treated with frusemide, amoxycillin, and dobutamine but she did not respond to these measures and died within eight hours of admission.

At necropsy the heart weighed 350 g (normal 250–400 g) and was macroscopically normal. Histological examination of the myocardium showed vacuolar and focal necrosis with an inflammatory reaction. The coronary arteries were normal. The airways contained frothy liquid and the lungs were moist on section with microscopic changes consistent with acute pulmonary oedema. The right adrenal gland was replaced by a phaeochromocytoma weighing 70 g with typical histology.

PATIENT 3

This 39 year old woman with long standing rheumatoid arthritis started getting "funny turns" in 1976 when she was 29. Episodes lasted between two and 30 minutes when she experienced palpitation, chest tightness, and breathlessness. She was extensively investigated and initially it was felt that her symptoms were caused by refractory supraventricular tachycardia. Subsequent electrophysiological studies showed an atrioventricular accessory pathway, although later it was thought that this could not explain her various symptoms and the different types of ventricular and supraventricular tachycardias seen on Holter monitoring. Urinary concentrations of 4-hydroxy-3-methoxymandelic acid were assayed on numerous occasions but were always normal. Provocation tests with glucagon and tyramine were also within normal limits.

Symptoms settled spontaneously but in May 1986 she was admitted to hospital unconscious, tachycardic, and tachypnoeic after being resuscitated after a sudden collapse at home. She was found to have gross pulmonary oedema and was deeply unconscious with evidence of anoxic brain damage. She died shortly after admission despite full supportive treatment.

At necropsy the heart size was normal (300 g) and the coronary arteries were widely patent. The air passages contained a moderate excess of frothy mucus. The lungs were collapsed with considerable frothy oedema and congestion. Histological examination of the heart showed multiple foci of myocardial cell necrosis and surrounding infiltration with acute inflammatory cells. A phaeochromocytoma weighing 200 g and 7 cm in diameter was found in the right adrenal gland.

PATIENT 4

A 44 year old woman who was 36 weeks' pregnant was admitted in October 1986 with hydramnios and an abnormal glucose tolerance test. Her first two deliveries had been normal and although the third had been uncomplicated the baby had spina bifida and died soon after birth. Subsequently she had three miscarriages (fetal ages between eight and nine weeks). In 1985 she was investigated for episodic palpitation which she had had for 20 years. Supraventricular tachycardia was documented and no cause was sought.

Labour was induced by artifical rupture of membranes because of the hydramnios but failed to progress. At subsequent caesarean section a live baby was delivered but postoperatively tachycardia, hypotension, and severe pulmonary oedema developed in the mother. She had a cardiac arrest but was successfully revived and transferred to the intensive care unit. Despite full cardiopulmonary support, she had a further cardiac arrest and died within 12 hours of the caesarean section.

At necropsy the heart size was normal (295 g). The valves and coronary arteries were completely normal. Myocardial histology showed focal necrosis and inflammatory cells. The airways and lungs showed changes consistent with pulmonary oedema. The right adrenal gland was replaced with a dark brown tumour weighing 125 g and histology showed this to be a phaeochromocytoma with haemorrhagic and necrotic areas.

PATIENT 5

A 69 year old retired quarry worker collapsed and died while working on his farm. A short time before he had complained to his family of feeling generally unwell and breathless. There was no relevant past medical history and the general practitioner's records showed him to be normotensive.

At necropsy the heart size was normal (375 g). The coronary arteries showed a few patches of atheroma and the aorta showed moderate atherosclerosis. Microscopic examination of the heart was not performed. Both lungs were oedematous. A tumour 7 cm in diameter was found attached to the posterior abdominal wall, near the bifurcation of the aorta. Histologically this was found to be a phaeochromocytoma.

PATIENT 6

This 48 year old crane driver was admitted to hospital in 1981 with sudden onset of gangrene of the left forefoot, headaches, and breathlessness. He was normotensive and had normal heart sounds. The chest *x* ray showed slight cardiomegaly and pulmonary oedema, which responded to conventional diuretic treatment. An attempted embolectomy via the left popliteal artery produced no clot and the possibility of a vasospastic phenomenon was considered. A few days later a left below knee amputation was performed and histological examination of this showed no evidence of arterial disease. After the operation he was referred to the physicians and had several further investigations including an electrocardiogram, echocardiogram, and measurement of urinary concentrations of 4-hydroxy-3-methoxymendelic acid—all were within normal limits.

One year after the initial presentation he had a left lumbar sympathectomy performed because of persistent problems with a cold blue stump.

A second exploration was attempted two years after the initial presentation because of continuing pain in the stump, with a view to excision of the long saphenous nerve. During the operation pulmonary oedema developed. Postoperatively his blood pressure was 110/70 mm Hg and the urinary concentration of metadrenaline was raised (8·2 μmol/l (normal <5 μmol/l)). A computed tomogram showed a right adrenal tumour. At operation a phaeochromocytoma measuring 4 × 5 cm was removed. He made a good postoperative recovery.

Discussion

Cardiovascular injury induced by sympathomimetic amines has been well recognised for some time in both humans and experimental animals.[7 8] It is also recognised that myocardial lesions produced by high doses of catecholamines are similar in all species including humans.[9] The finding of foci of myocardial cellular necrosis is consistent and predominant. Initial lesions show diffuse oedema and minor alteration of myocardial nuclei. Later, focal myofibril degeneration with loss of striation of individual myocytes is seen.[10] Inflammatory cellular infiltration takes place in response to this. When phaeochromocytomas were transplanted into rats the heart consistently showed multifocal lesions of enhanced interstitial and replacement fibrosis, granularity of the cytoplasm and contraction band necrosis, and mixed inflammatory infiltrates six weeks after transplantation.[11] More advanced lesions had more fibrosis and did not show inflammatory cells.[10]

During the earlier stages, the myocardium in patients with phaeochromocytomas resembles that seen in patients treated with noradrenaline (norepinephrine) and the term "norepinephrine myocarditis" has been used to describe the cardiac lesion.[7, 12] Others have used the same term because of functional improvement in the cardiac condition after surgical removal of the phaeochromocytoma.[13] It is perhaps more appropriate to use only the term "focal myocardial necrosis" because the inflammation is always a secondary process[14] or "catecholamine induced cardiomyopathy" which is the term that we have used. Previously it has been suggested that the incidence of clinically significant catecholamine induced cardiomyopathy is far less than that seen at necropsy.[15]

Studies of catecholamine induced cardiomyopathy have shown a global reduction in myocardial pump function caused by a combination of down-regulated β receptors and a net reduction in viable myofibrils.[16] Rabbit hearts with catecholamine induced cardiomyopathy had a reduced inotropic sensitivity to noradrenaline and also a reduced response to calcium chloride infusion. The pathogenesis of catecholamine induced cardiomyopathies is probably multifactorial. Catecholamine induced vasospasm leading to hypoxia is implicated and supported by the finding that more severe lesions are located near the cardiac apex—an area of peripheral coronary circulation.[17] Excess noradrenaline also induces changes in permeability of the sarcolemmal membrane leading to increased calcium influx. This excess intracellular calcium has a direct toxic action giving rise to cellular necrosis. Although calcium is undoubtedly important, it is not the exclusive factor causing damage.[18, 19] There is evidence that the oxidised products of catecholamines may be toxic and contribute to the damage.[19] It has also been proposed that the injury process might involve damage by free radicals.[20]

The commonest manifestations of phaeochromocytoma are of paroxysmal or sustained hypertension or symptoms of paroxysmal adrenergic stimulation, such as palpitation, headaches, anxiety, sweating, and tremors; rarer presentations, such as acute abdomen, cerebrovascular events, myocardial infarction, hyperglycaemia, postural hypotension, shock, and heart failure have been reported.

We described five normotensive patients with phaeochromocytoma presenting with pulmonary oedema as a dominant feature. In the patient who died suddenly pulmonary oedema was seen at necropsy. None had confirmed hypertension. Five of the patients had normal sized hearts. Histological examination undertaken in four of our patients showed extensive focal myocardial necrosis.

The diagnosis of phaeochromocytoma was considered in two of the six patients described. One gave a history of paroxysmal symptoms before presenting with severe heart failure as a terminal event (patient 3); the other had additional vascular spasms together with pulmonary oedema (patient 6). Both of these patients had normal urinary concentrations of 4-hydroxy-3-methoxymandelic acid initially but neither was examined by computed tomography when they first presented and this investigation might have led to the correct diagnosis being reached earlier. In patient 6, a subsequent computed tomogram confirmed the presence of an adrenal phaeochromocytoma. We now use computed tomography in the initial assessment of patients in whom the diagnosis of phaeochromocytoma is strongly suspected despite normal urinary concentrations of 4-hydroxy-3-methoxymandelic acid. The remaining four patients presented rapidly and died before relevant investigations could be performed.

Our experience indicates that phaeochromocytomas cause clinically important catecholamine induced cardiomyopathy more commonly that has been thought. In patients with phaeochromocytoma presenting with acute heart failure the prognosis can be very poor because of the extensive focal myocardial damage.

In patients presenting with heart failure without any obvious cause, the diagnosis of phaeochromocytoma should be considered. Urinary concentrations of 4-hydroxy-3-methoxymandelic acid should be measured and computed tomography should be undertaken as soon as possible.

We thank the following consultants for the inclusion in this report of patients under their care: Dr A J Marshall, Dr E W Hughes, Dr B J Prout, and Dr J L Dunscombe.

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VIEWS FROM THE PAST *William Evans*

William Evans's obituary was printed in the *British Heart Journal* of January 1989. Here he is photographed by me in 1975 on his farm in Tregaron, Cardiganshire, where he was born in 1895 and died in September 1988, aged ninety two. Wallace Brigden, writing in Munk's Roll, says that "On retirement from the London Hospital he returned to the Wales he loved. The Principality reciprocated in making him High Sheriff of Cardigan and an Honorary Druid. He placed both of these honours above the legion of professional ones which came his way. He was not the most eminent cardiologist of his time but one of the most unusual, well known and well liked. In retrospect, medicine in general and cardiology in particular seemed to be only an interlude, albeit an absorbing and exciting one which occurred between childhood in the Teify Valley overlooked by Cambrian hills and the same unchanged scene in his twenty five years of retirement."

AUBREY LEATHAM

Br Heart J 1990;63:238–45

Balloon dilatation of the aortic valve in a pulsatile flow model: assessment of the mechanisms and the magnitude and duration of changes in valve area and gradient

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Abstract

Eighteen stenotic aortic valves (17 removed at operation) mounted in a pulsatile flow duplicator were dilated with a balloon catheter. Sequential measurements showed that the valve area initially increased from a mean (SD) of 0·52 (0·16) to 0·78 (0·17) cm^2. It was 0·73 (0·16) cm^2 five minutes after dilatation and this was little changed at four weeks (0·70 (0·15) cm^2). Initially the mean transvalvar gradient fell significantly from 54 (27) to 32 (8) mm Hg but increased to 35 (10) mm Hg at five minutes and to 40 (11) mm Hg at four weeks. In six valves stretching of the orifice was the only mechanism responsible for the changes while in the remainder there was tearing through commissures with a greater initial increase in area (0·31 *v* 0·18 cm^2) and a smaller decrease in area at five minutes (0·03 *v* 0·08 cm^2). Fractures of calcific deposits in non-commissural positions were seen in one valve only.

This laboratory study of isolated aortic valves showed a significant but small increase in valve area after balloon dilatation, which was greater when commissural tearing had occurred. Recoil of the stretched orifice was complete at five minutes and there was little further change over the next four weeks.

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Percutaneous balloon dilatation of the aortic valve in elderly patients with calcific aortic stenosis deemed to be at high risk from conventional operation was first described as a palliative procedure by Cribier *et al* and McKay *et al* in 1986.[1 2] Their initial encouraging reports were soon followed by larger studies with more impressive results.[3–5] Other reports suggested only a very limited effect from balloon dilatation[6] and provided evidence of a rapid loss of any haemodynamic improvement.[7] Recent studies showed that more than half the patients had died, undergone valve replacement or redilatation, or had a recurrence of symptoms at mean follow up periods of 5–8 months[8–11] and the value of the procedure remains uncertain.

Haemodynamic evaluation of dilatation of the aortic valve is confounded by several procedural factors including myocardial depression during balloon inflation, haemorrhage, arrhythmias, and vagal effects. Aortic valve area estimations by the Gorlin formula may be unreliable at discriminating small changes, especially in patients with low cardiac outputs, and the timing of non-invasive assessments has varied between studies.

Both the procedural and methodological limitations to haemodynamic assessment have contributed to uncertainty about the real and apparent effects of the procedure. Intraoperative simulation was limited to single measurements before and after dilatation[6] and like most in vitro studies[12 13] did not measure areas and gradients during flow. We performed balloon dilatation in 18 stenotic human aortic valves mounted in a pulsatile flow duplicator and measured the sequential changes in area and gradient without the constraints present in clinical practice.

Patients and methods

VALVES

Of the 18 valves, seventeen were removed intact at aortic valve operation and one at routine necropsy. Fourteen valves were stored in 10% formaldehyde while four were used fresh from operation and thereafter stored in homograft valve nutrient solution.[14] Preoperative peak to peak catheter gradients ranged from 50 to 130 mm Hg and significant aortic regurgitation was present in only three patients. Eleven valves were bicuspid, six tricuspid, and one unicuspid. In two patients percutaneous balloon dilatation had been performed without sustained symptomatic improvement (table 1).

TEST APPARATUS

The pulsatile flow duplicator[15] consisted of a roller pump connected to a pulsatile control unit (Stockert Shiley model PFC II; Shiley Ltd, Berkshire) that continuously recirculated saline from a 10 litre reservoir through the stenotic valves when placed in the test chamber (fig 1). The valves were mounted with silk sutures and cyanoacrylic glue on to a truncated polyvinyl chloride cone, cut to the diameter of the valve ring, and the 40 mm diameter base was then clamped into the test chamber. The test chamber had a translucent end plate with eight radial flow outlet ports arranged symmetrically around the circumference, allowing a centrally placed video camera (Hitachi GP 5E/1E; Hitachi Ltd, Tokyo, Japan) to be

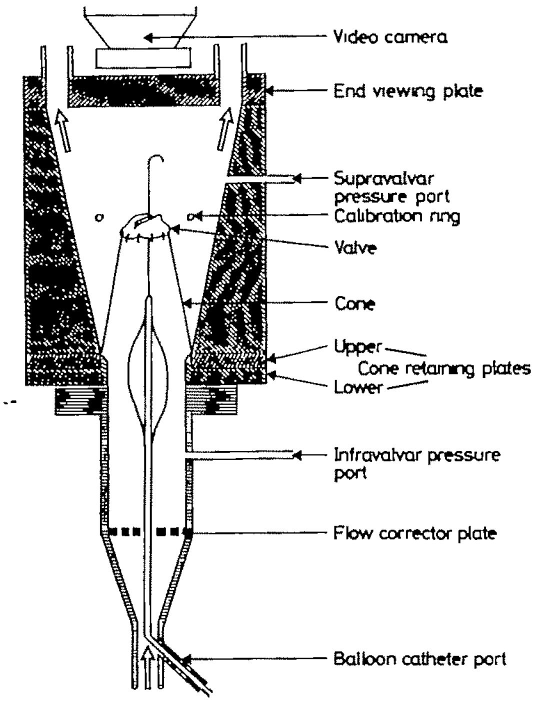

Figure 1 Cross section through the test chamber containing a valve mounted on to a cone fixed in place by the cone retaining plates. Saline at 37°C was continuously pumped at 4 l/min through the valve in the direction indicated by the arrows. The saline left the chamber via radial outlet ports placed symmetrically around the video camera which had an unobstructed view of the valve during flow.

aligned above the valve. The magnified image of the aortic valve was displayed on a video monitor and stored on video tape (Racal Store 7; Racal Recorders, Southampton). The maximal aortic valve area was then measured by planimetry from the monitor screen with a bitpad (Bit Pad 1 digitiser tablet; Summagraphics, Fairfield, USA) interfaced to a Commodore computer (Model 4032; Commodore, USA). A calibration ring set at valvar level was used for reference. Pressure ports in subvalvar and supravalvar positions allowed measurement of the mean transvalvar gradient by substraction of the integrated pressure-time curves (Hewlett Packard models HP 1209 A and HP 7754 B). The saline was maintained at 37°C (1°C) and delivered at a constant output of 4 litres per minute with an ejection period of 45% and repetition rate of 70 per minute. The model is capable of delivering up to 5 4 litres per minute but was set at the lower level to reduce the stresses on the valves which were due to undergo repeated measurements. We showed that the valve area of stenotic valves in this model was maximal at a flow of 3 litres per minute.[15]

PROCEDURE

The mounted valve was placed in the test cell and saline was circulated for 30 minutes (allowing equilibration of temperature and dissolved gases) before the valve area and mean transvalvar pressure gradient were measured. A 20 mm balloon (Meditech, USA) was advanced anterogradely through the valve over a 0·35 inch J guide wire and positioned with the centre of the balloon inside the valve orifice as seen from the side view. The balloon was inflated to 3 atmospheres (303 kPa) (manufacturer's limit) during continuous video recording. When obvious commissural tearing occurred the balloon was deflated after 30 seconds; otherwise inflation was maintained for a full minute. During inflation the circulation was temporarily stopped to avoid pressure overload to the circuitry and valve and the circulation was restarted on deflation. Five seconds after the flow had been re-established we measured the valve area and gradient. These measurements were repeated at 5, 10, 15, 20, 25, 30, 60, and 120 minutes while the flow was maintained continuously. The valve was removed from the chamber and stored in the appropriate medium. At 24, 48, and 72 hours and at 1, 2, and 4 weeks the valve was returned to the test chamber and, after 30 minutes of flow, the area and gradient were measured as before. In two valves complete data were not obtained and in one video recordings were inadvertently erased during subsequent recordings.

RADIOGRAPHY

Valves were examined by projection microradiography with a Hilger Watts generator (London) before and after balloon dilatation. The images produced were 3·5 times real size and showed the calcific deposits in fine detail.

DATA ANALYSIS

Changes in valve area and mean pressure gradient were investigated by an analysis of variance for repeated measures with a Genstat Package on the University of London main frame computer. The results are expressed as means (SD) and a p value $<0·01$ was considered statistically significant.

Results

AREA AND GRADIENT CHANGES

There was an increase in valve area and decrease in the mean pressure gradient across all the valves studied (table 1). The aortic valve area increased from 0·52 (0·16) cm^2 to 0·78 (0·17) cm^2 immediately after balloon dilatation ($p < 0·001$) but had fallen to 0·73 (0·16) cm^2 five minutes after the procedure ($p < 0·01$). Thereafter there were no significant changes in valve area and at four weeks the area measured 0·70 (0·15) cm^2—35% more than before dilatation. The mean transvalvar pressure gradient fell from 54 (27) mm Hg to 33 (8) mm Hg immediately after the procedure ($p < 0·001$) rising to 35 (10) mm Hg at five minutes (NS), with a further slight rise to 40 (11) mm Hg at four weeks ($p < 0·01$ compared with dilatation after). Values at times between those reported were similar, did not affect the statistical analysis, and have been omitted for clarity (fig 2).

MECHANISM OF DILATATION

The balloon totally occluded the orifice (figs 3 and 4) of only five valves (one tricuspid, one unicuspid, and three bicuspid). In six valves

Table 1 Patient and valve characteristics and results of balloon dilatation

							Aortic valve area (cm²)				*Mean pressure gradient (mm Hg)*			
No	*Age*	*Sex*	*Gradient**	*AR*	*Type*	*Mechanism*	*Before*	*After*	*5 min*	*4 wk*	*Before*	*After*	*5 min*	*4 wk*
1	62	M	80	0	B	Stretch	0·67	0·87	0·77	0·75	45	38	43	40
2	68	M	80	1	B†	Stretch (O)	0·69	0·83	0·76	0·72	44	38	40	42
3	73	M	70‡	1	B	Split (O)	0·65	0·82	0·83	0·77	58	36	40	38
4	54	M	90	1	T	Split	0·59	0·90	0·87	0·85	36	22	22	26
5	73	M	50	0	T†	Stretch	0·48	0·73	0·66	0·63	40	29	31	36
6	82	F	¶	¶	T	Stretch (O)	0·24	0·49	0·42	0·40	67	46	53	58
7	71	F	—	0	B†	Split (O)	0·34	0·70	0·61	0·58	82	36	38	49
8	47	M	80	1	B	Split	0·55	1·06	1·01	0·82	31	20	20	31
9	48	M	55	1	T	Split	0·60	0·81	0·80	0·81	44	27	27	33
10	30	F	80	1	B†	Split	0·39	0·75	0·70	0·66	53	29	29	36
11	62	M	65	1	T	Split	0·52	0·68	0·64	0·64	53	33	40	44
12	69	M	70	2	T	Stretch	0·36	0·45	0·40	0·40	42	36	42	42
13	35	F	95	2	U	Split (O)†	0·51	0·81	0·76	0·76	53	31	31	33
14	54	M	70	0	B	Split	0·56	0·66	0·65	0·67	53	47	49	49
15	61	M	55	2	B	Stretch	0·90	1·04	0·97	0·91	29	24	24	31
16	55	M	130	1	B	Split§	0·24	0·68	0·67	0·57	149	40	42	71
17	76	M	130	1	B	Split	0·53	0·76	0·76	0·73	47	33	35	33
18	69	M	70‡	0	B	Split	0·53	1·01	0·92	0·91	49	22	24	28
Mean	61		87				0·52	0·78	0·73	0·70	54·2	32·6	35·0	40·0
(SD)							(0·16)	(0·17)	(0·16)	(0·15)	(26·8)	(7·9)	(9·5)	(11·3)

*Peak to peak at diagnostic catheterisation.
†Specimen preserved in homograft nutrient medium.
‡Balloon dilatation performed in vivo
§Pre-dilatation with 9·0 mm balloon
¶Postmortem valve.
AR, aortic regurgitation; B, bicuspid, O, orifice totally occluded; T, tricuspid, U, unicuspid valves.

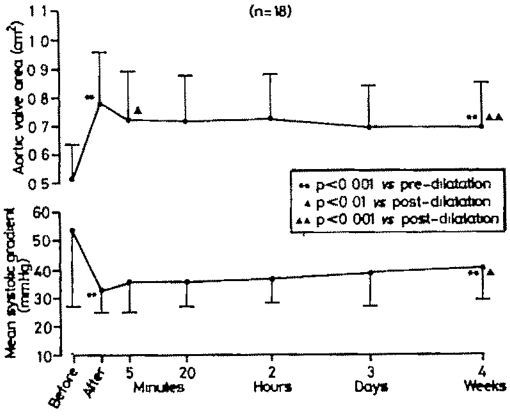

Figure 2 Aortic valve area (cm²) and mean systolic transvalvar gradient (mm Hg) plotted against time. Each point represents the mean and the bar the standard deviation.

there were substantial passages (fig 5) around the balloon (up to 60% of the original orifice) (three tricuspid and three bicuspid) while in the remainder only insignificant apertures (<20% of orifice) were present (fig 6). Stretching of the valve orifice was the sole mechanism (figs 3, 4, and 5) in six valves (four tricuspid and two bicuspid) and there was commissural tearing or splitting in 12 valves (figs 6 and 7). Though the valves with splitting had a greater immediate increase in valve area (0·31 *v* 0·18 cm²) and fall in valve gradient (28 *v* 9 mm Hg) than the valves that only showed stretching, these differences did not achieve statistical significance (table 2). Valve areas >1·0 cm² were seen in only three valves all of which had tearing through commissures. In one heavily calcified valve the deflated 20 mm balloon could not pass through the orifice. Dilatation with a 9 mm balloon allowed subsequent dilatation with the larger balloon and the final valve area was more than doubled. Neither of the two (bicuspid) valves in which clinical balloon dilatation had been performed showed macroscopic changes attributable to the procedure but both were easily split in vitro. In only one valve was there clearly a fracture of non-commissural calcium (fig 8) while fractures of commissural calcium deposits were found in seven with commissural splitting.

Discussion

Interventional balloon techniques are currently applied to a range of cardiovascular diseases. The favourable results obtained with coronary angioplasty and dilatation of congenital valve obstructions have lead to the extension of balloon dilatation to mitral and aortic stenosis in adults.[16 17] Mitral valvotomy is a well established surgical technique and balloon dilatation in many ways mimics this effective procedure. In contrast, the poor long term results of operative aortic valvotomy[18] mean that many, especially surgeons, doubt the effectiveness of balloon dilatation of such heavily calcified valves.

Immediately after aortic valve dilatation patients are haemodynamically unstable so that the interpretation of changes produced by the procedure is difficult. In particular, myocardial depression during balloon inflation (owing to ventricular overload and coronary underperfusion) may lead to underestimation of the measured gradient. In addition, haemorrhage, arrhythmias, vagal stimulation, and contrast administration may all affect the haemodynamic indices. The Gorlin formula may underestimate aortic valve area in low output states,[19] which are often present in these patients, but more importantly its sensitivity to small changes in aortic valve area is unknown. In the days after balloon dilatation haemodilution and/or transfusion effects may variably alter blood viscosity, cardiac output, and ejection dynamics. Thus even the optimal timing for the early non-invasive assessment is uncertain.

Reports of apparent increases in calculated valve area in the days after balloon dilatation[20]

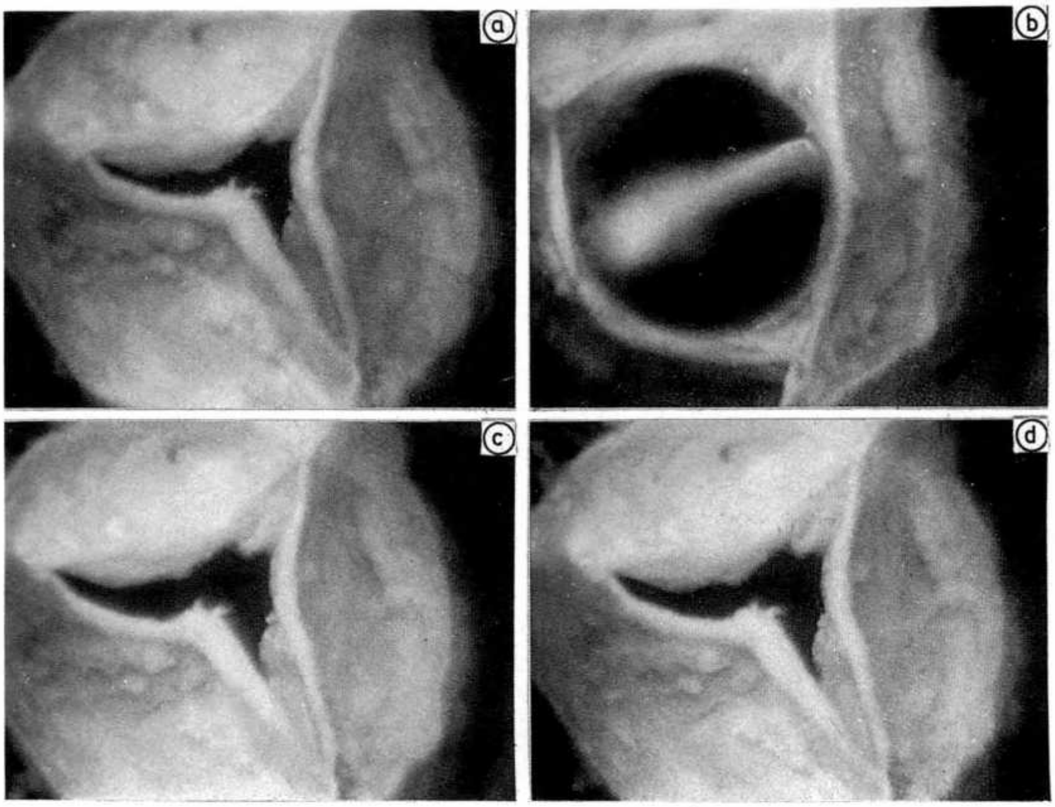

Figure 3 Senile tricuspid valve (No 6) obtained at necropsy with an aortic valve area of 0·24 cm² (a). The 20 mm balloon completely occluded the orifice (b) and on deflation valve area had increased to 0·49 cm² (c). By five minutes there has been some recoil and the area measured 0·42 cm² (d). Unless otherwise indicated all frames in this and subsequent figures were taken during systole.

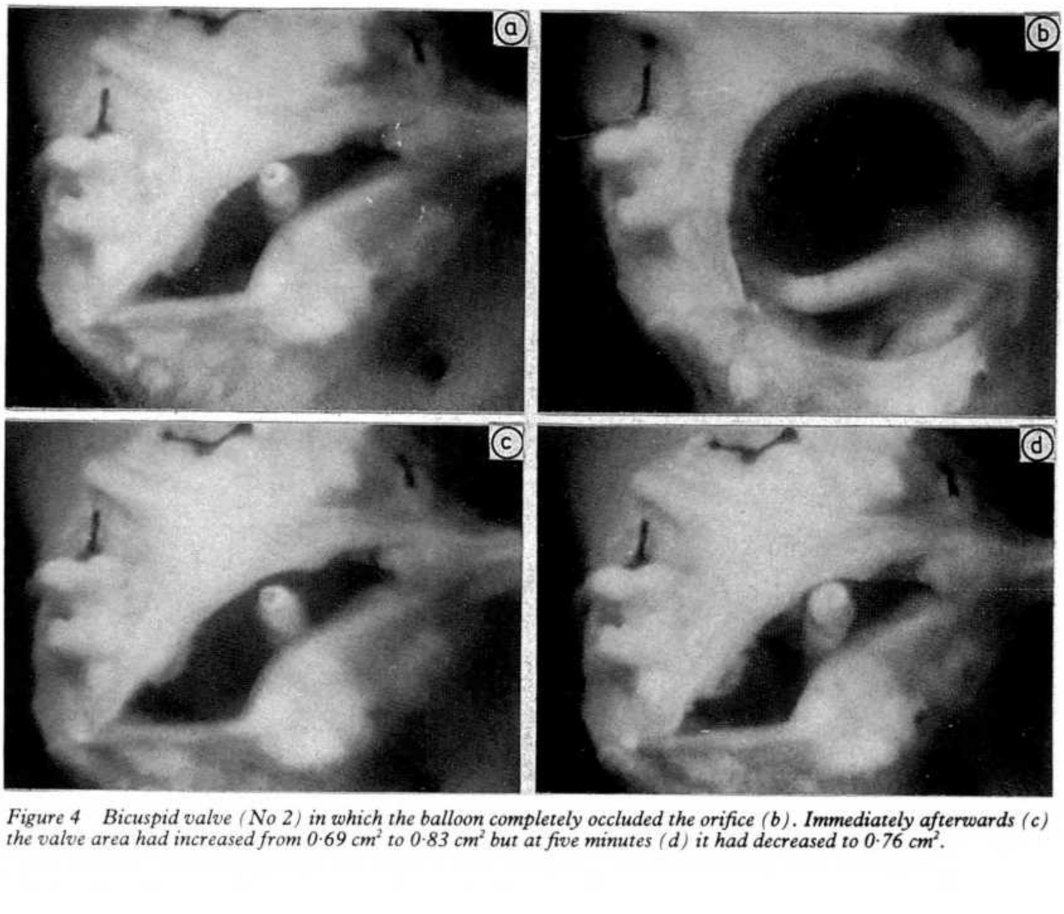

Figure 4 Bicuspid valve (No 2) in which the balloon completely occluded the orifice (b). Immediately afterwards (c) the valve area had increased from 0·69 cm² to 0·83 cm² but at five minutes (d) it had decreased to 0·76 cm².

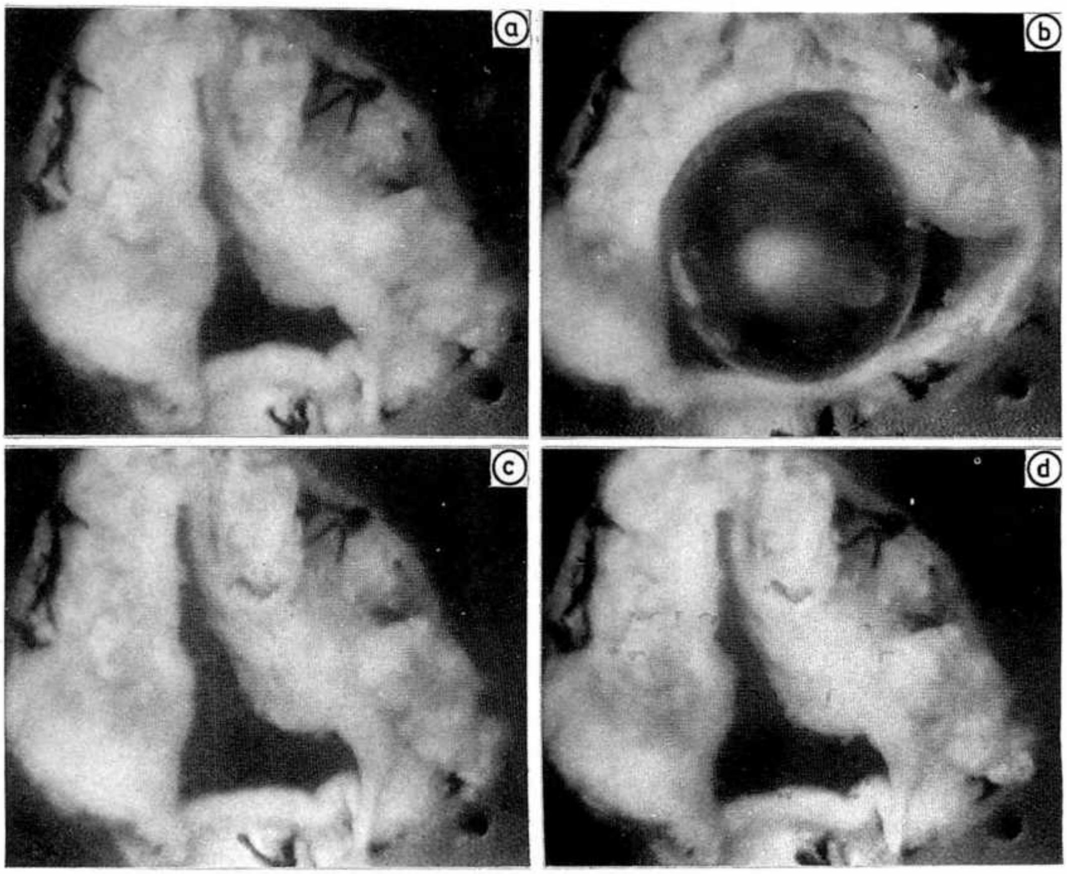

Figure 5 Tricuspid valve (No 5) in which the inflated balloon (b) did not occlude the orifice and the areas at the commissural angles totalled 60% of the original orifice area. On deflation the valve leaflets rapidly returned towards their original position (c) although the area had increased from 0·48 cm² to 0·73 cm². At five minutes (d) the area had decreased to 0·66 cm².

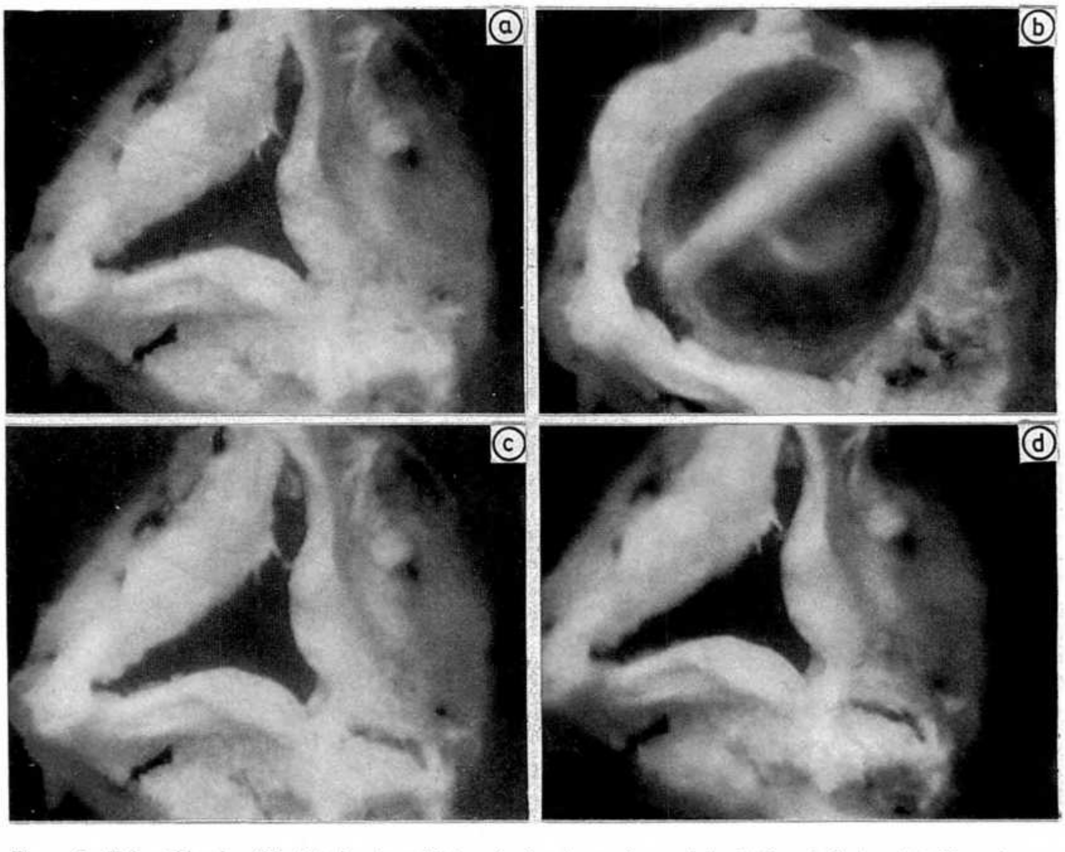

Figure 6 Tricuspid valve (No 11) showing splitting of a fused commissure during balloon inflation (b). The valve area increased from 0·52 cm² to only 0·68 cm² after dilatation (c) and at five minutes had recoiled to 0·64 cm² (d).

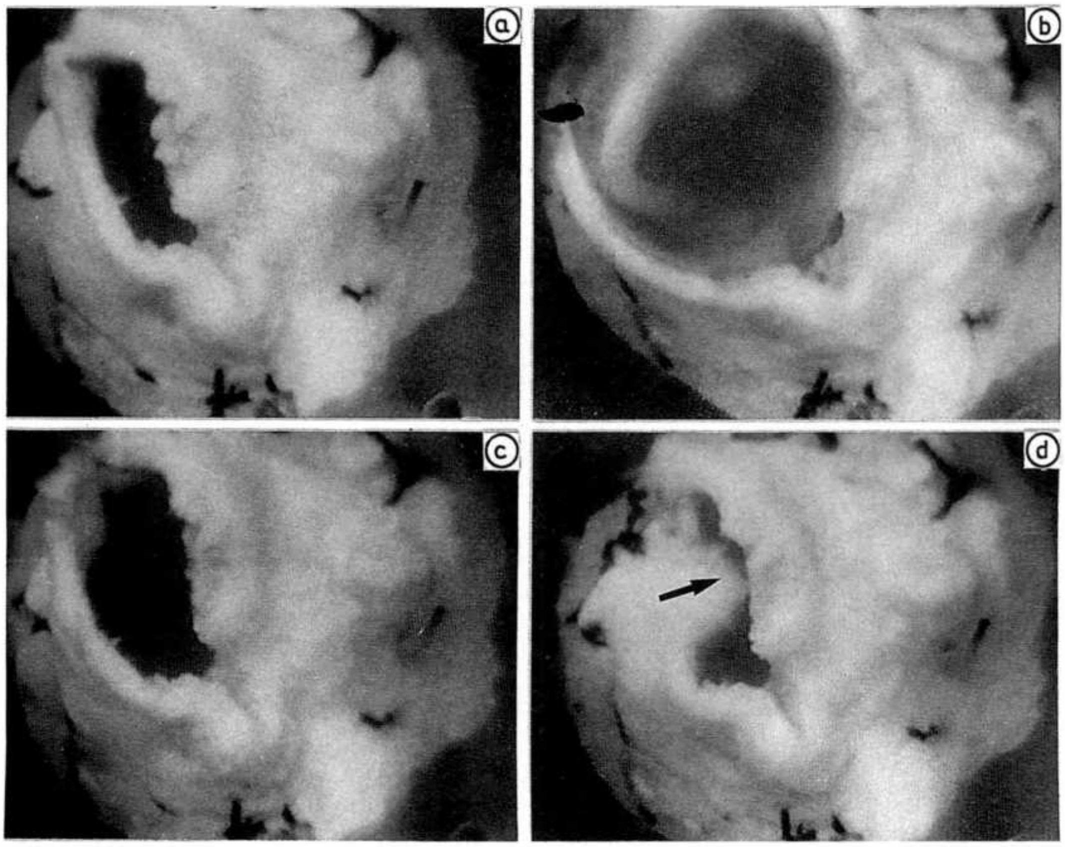

Figure 7 Bicuspid valve (No 10) with an orifice area of 0·39 cm² (a). There is tearing of both commissures during inflation but especially of the commissure at the top left (b). The valve area had increased to 0·75 cm² (c) and the diastolic frame (d) shows the tear and a flail leaflet (black arrrow).

Table 2 Area and gradient changes (mean (SD) according to mechanism of dilatation

		Aortic valve area (cm²)			
	n	*Before*	*After*	*5 min*	*4 wk*
All	18	0·52 (0·16)	0·78 (0·17)	0·73 (0·16)	0·70 (0·15)
Stretching	6	0·56 (0·24)	0·74 (0·23)	0·66 (0·22)	0·64 (0·20)
Splitting	12	0·50 (0·12)	0·80 (0·13)	0·77 (0·12)	0·73 (0·11)
		Mean systolic gradient (mm Hg)			
	n	*Before*	*After*	*6 min*	*4 wk*
All	18	54·2 (26·8)	32·6 (7·9)	35·0 (9·5)	40·0 (11·3)
Stretching	6	44·5 (12·4)	35·2 (7·7)	38·8 (10·1)	41·5 (9·1)
Splitting	12	59·0 (30·9)	31·3 (8·0)	33·1 (9·0)	39·3 (12·5)

are countered by reports of decreases[7,11] and both are explained on the basis of changes in left ventricular function. Cardiac output is variously reported to be decreased,[11] unchanged,[21] or increased[3,5,8] immediately after the procedure. The procedural effects are likely to vary considerably between patients, depending on their initial left ventricular function and the severity and morphology of their stenotic valve. Variation between centres with their differing techniques, equipment, and experience may also influence these variables while the methodological errors in both invasive and non-invasive assessment will vary according to the timing of the measurements. Serial measurements in consecutive patients have not been reported owing to the variable numbers at any point in follow up and because frequent invasive assessment is inappropriate. These considerations prompted our study of the immediate and short term effects of valve dilatation in vitro.

We found only small changes after balloon dilatation—the magnitude of which was less than that reported in several large clinical series.[3,8,10,21] In vitro there was almost an immediate recoil of the stretched orifice (whether or not commissural tearing had occurred) but after 5 minutes there was little further recoil. Those studies in patients that show a rapid loss of the haemodynamic gain[7,11] are likely to be overestimating the immediate benefits and their subsequent measurements are probably a better indication of the immediate effect. The very small changes seen in these patients may reflect inadequate balloon positioning but they would also accord with the valves in which we found no commissural tearing and where gains in area were smaller. It may be that serial assessments would have shown similar findings in many of the patients reported to show "restenosis" by Doppler techniques a few months after dilatation.[10,11] Postmortem and operative evidence after valve dilatation indicate that commissural tears or fractures persist for some months at least[11,22–24]; it seems that in isolation stretching or "microfractures" or both do not produce lasting benefit.

LIMITATIONS

The valves obtained at operation were included only if they were removed in a single piece and without damage. Obviously the true aortic valve annulus was not removed and the suture line to the unyielding cone was only an approximation of the in vivo annulus. This may have influenced the results in two opposing directions. A more compliant annulus might

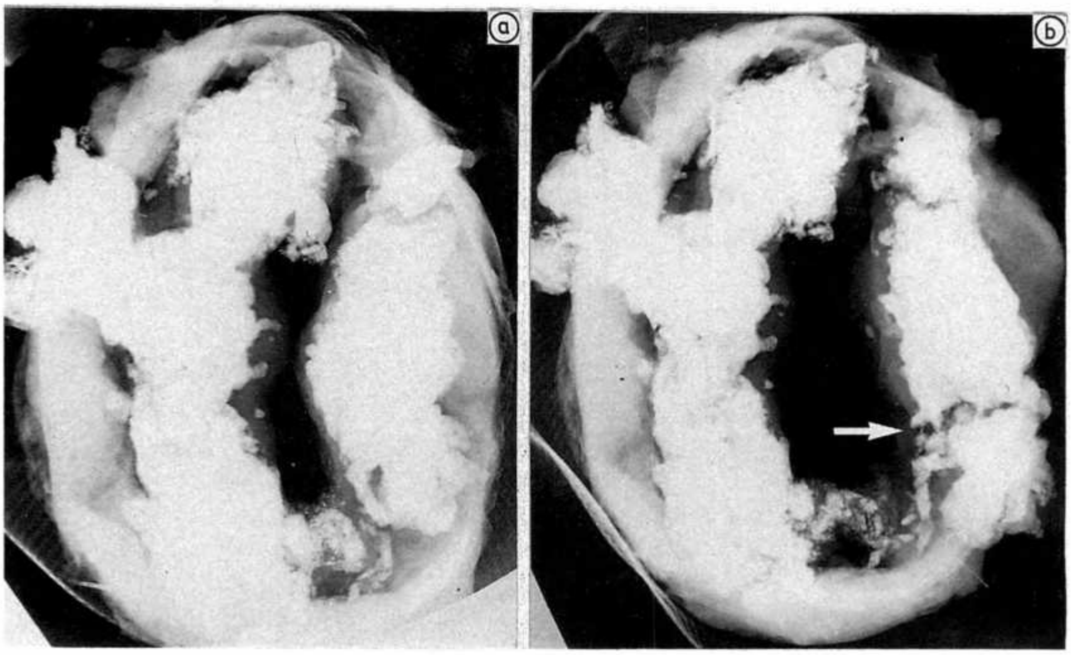

Figure 8 Bicuspid valve (No 18) with splitting through both commissures. There was fracturing of calcium in the commissures but in addition a clear fracture of non-commissural calcium (white arrow) (b). The valve mounting cone appeared as a faint grid with a denser ring where the material was folded.

have prevented tearing through the commissure to the edge of the specimen and so resulted in a smaller orifice area. But at the same time the effect of more force on the remaining parts of the orifice may have caused more stretching, tearing of other commissures, or fractures of calcific deposits and so produced a larger orifice area. In six of the valves (including the necropsy specimen with a true annulus) only stretching was evident and changes were much smaller than in the other valves showing commissural tearing—so on balance it seems that the absence of the annulus might if anything have exaggerated the effects. Ideally, we should have studied postmortem valves with the annulus en bloc but during the nine month study period we found only one suitable case at routine necropsy.

The valves were obtained from a representative group of patients undergoing aortic valve operation who are not typical of patients undergoing balloon dilatation.[3 8-11 16 19] Our patients were thus younger and this accounts for a higher frequency of men and bicuspid valves. The pattern of calcification is different in bicuspid and tricuspid valves and this may partly explain why we found fewer fractures in calcific deposits than in some,[12 13 22-24] though by no means all, postmortem or operative studies.[6 7 11]

We used a 20 mm balloon in this study for a single (though optimally positioned) inflation. In some valves the balloon seemed to be too large and split the "annulus" whereas in those that showed stretching alone it may have been too small. Most clinical procedures, however, have been with 20 mm or smaller balloons and an increase in the balloon size has not always increased valve area after clinical recurrences.[8] Nevertheless, it is possible that the much larger balloons being used by some more recently would have improved the results in some of our valves.

Leaflet recoil caused an early fall in valve area and only later a rise in gradient. The supravalvar pressure port in this model is at a fixed distance from the retaining plates that hold the cones, and the distance from the valve to the pressure port varied according to the length of cone left after it was cut down to accommodate the valve annulus area. The distance was nearly always greater than a half of the orifice diameter[15]—that is the distance at which the pressure drop is lowest (vena contracta)—so that slight though systematic under reading of the gradients may have reduced the extent of the early changes. The valve area, however, is not the only factor to determine the gradient—orifice geometry and depth are other factors.[25] The orifice depth is likely to have increased as the stretching displaced leaflet material and reduced the expected fall in the gradient; recoil of the leaflet thickening would then have offset the rise in gradient. Most of the valves were preserved in formalin—a storage medium used by others for valve dilatation studies[12 13 26]—and the effects of formalin may provide an alternative explanation for the gradient changes. We have previously shown that the valve area and gradient measured over a wide range of flows does not change within a month of explantation and storage in either formalin or nutrient solution.[15] Nevertheless formalin storage may have had an effect on the gradient measured across *dilated* valves, though the four valves used fresh from surgery (and thereafter stored in nutrient solution) behaved in a similar fashion.

CONCLUSIONS

We found significant though rather small increases in valve area after balloon dilatation of calcific stenotic aortic valves. Commissural splitting seemed to increase the orifice area more than stretching alone, but fractures of calcific deposits unrelated to commissures were uncommon. Stretching of the valve orifice was followed by a measurable recoil within the first five minutes, irrespective of coexistent commissural splitting. Thereafter, and in the absence of any reparative mechanisms that might be present in vivo, there were no significant changes in valve area over the succeeding four weeks. Assessment of balloon dilatation of the aortic valve in the clinical setting should be performed only when the patient is stable and all the procedural effects can be discounted. In that way it might be possible accurately to document the real effects of the procedure. The changes that we saw suggest that patients who are critically compromised by aortic stenosis may benefit from balloon dilatation. In most patients, however, the improvement in valve area is unlikely to be adequate for definitive treatment.

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Br Heart J 1990;63:246–8

CASE REPORTS

Embolisation of a complex coronary arteriovenous fistula in a 6 year old child: the need for specialised embolisation techniques

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Abstract

Transcatheter embolisation was performed in a six year old child with a large haemodynamically significant arteriovenous fistula between the left coronary artery and right ventricle. The fistula seemed to fill via a single large septal branch of the left anterior descending coronary artery. This was occluded distally with a detachable balloon backed up by a proximal coil. After this the flow through the fistula was considerably reduced but it still filled via a small diagonal branch that had not been noted previously. This branch was subsequently occluded in its most distal part by a coaxial catheter technique and a single microcoil. Complete occlusion of the fistula was produced and there were no complications.

Despite the recent development of interventional procedures in congenital heart disease and the increasing use of embolisation techniques there are few descriptions of embolisation of coronary arteriovenous fistulas and malformations.[1,2] Most reviews of interventional procedures in congenital heart disease make no mention of embolisation of coronary artery anomalies.[3,4] We have previously described cases in which embolisation by a detachable balloon was used to occlude large coronary arteriovenous fistulas.[1,2] We describe a further unusual case in a six year old child who had a complex arteriovenous fistula with a dual supply that needed two different embolisation techniques to achieve complete occlusion.

Case report

A six year old Nigerian boy was found to have a murmur when he was a year old, when he was examined after a chest infection. The murmur was continuous with accentuation in diastole and was best heard at the lower left sternal border. Otherwise he was symptom free, active, and thriving.

Cardiac catheterisation was performed when he was three years old. Pulmonary artery pressure was 38/12 (mean 24), right ventricular pressure 40/10, and aortic 90/50 (mean 65) mmHg. Oximetry showed a left to right shunt (Qp:Qs 2·5:1). Aortography showed a fistula between the left anterior descending coronary artery and the apex of the right ventricle.

When he was six years old his resting electrocardiogram and chest radiograph were normal. A first pass radionuclide scan showed the left to right shunt (2·6:1).

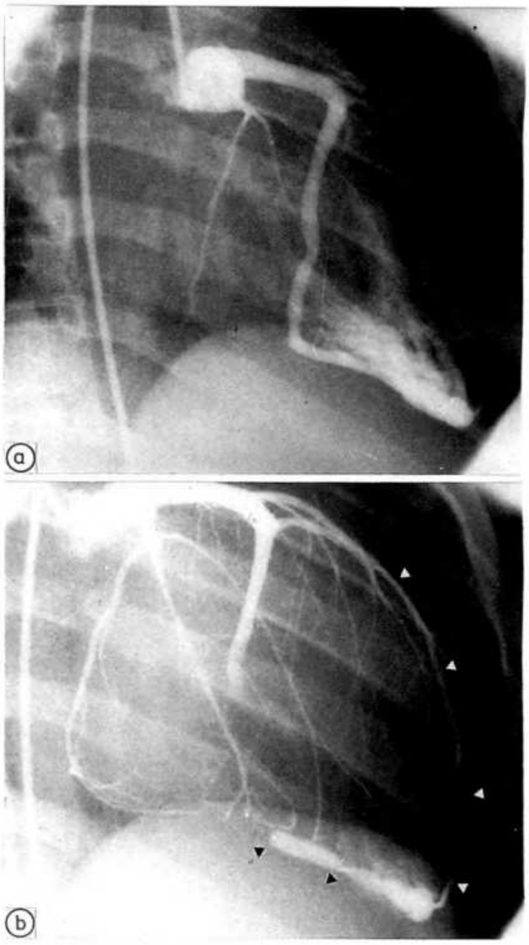

Figure 1(a) Selective left coronary arteriogram (right anterior oblique view) that shows a single large septal branch arising from the proximal anterior descending artery and communicating with the right ventricle. Note the poor filling of the other branches of the left coronary caused by the steal effect. (b) A contrast filled detachable balloon (black arrowheads) has occluded the fistulous artery in a distal location. Despite this and considerably reduced flow the fistula is still filled by a much smaller diagonal branch (white arrowheads). This is now shown much more clearly that in (1a).

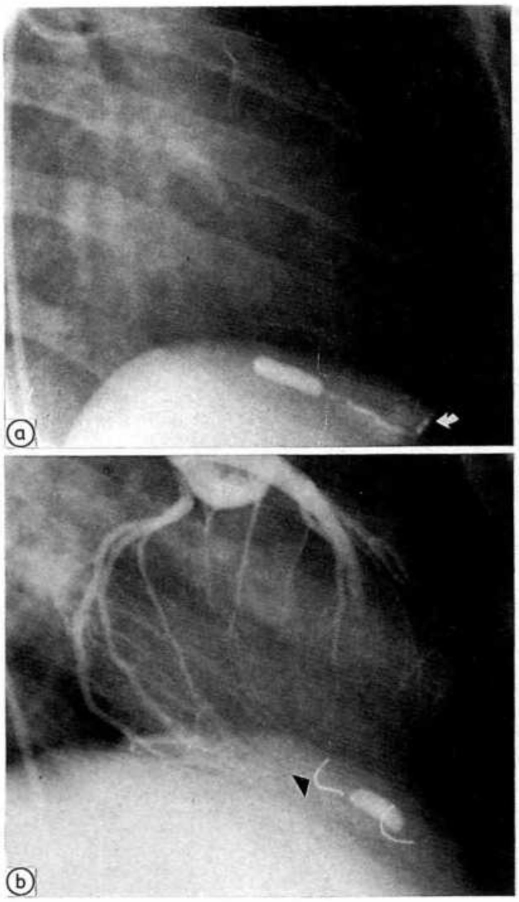

Figure 2 (a) A coaxial 3F catheter has been passed into the distal part of the small diagonal branch. A metal marker identifies its tip (white arrow). The limited injection of contrast that is possible through this very small catheter opacifies the fistula. (b) Post embolisation. A further microcoil has been placed immediately proximal to the balloon (arrow). The second coil is at the apex of the heart adjacent to the fistula. Note the much better filling of the normal coronary branches after occlusion of the fistula.

EMBOLISATION PROCEDURE

A 6F catheter was positioned in the proximal left coronary artery via the femoral artery and under general anaesthesia. Coronary arteriography showed a large septal branch passing to the posterior interventricular groove and then forwards to drain into the right ventricle (fig 1a). Through this we guided the 2/3F balloon catheter delivery system with an attached detachable latex balloon (Ingenor, Paris) into the large artery to a position just proximal to the fistula. A test inflation of the balloon showed that it produced complete occlusion and there were no untoward clinical effects or electrocardiographic abnormalities. The balloon, filled with dilute contrast medium, was then detached. A post embolisation cineangiogram showed occlusion of the large septal artery but some residual filling of the fistula via a much smaller and previously unrecognised diagonal branch arising from the anterior descending artery (fig 1b). We used a 3 French coaxial catheter (Tracker 18) (Target Therapeutics) and a steerable 0·014 inch coronary guide wire to catheterise this branch selectively so that the tip of the 3F catheter was immediately proximal to the site of the fistula (fig 2a). A single platinum coil (Hilal 1·5 cm length) (William Cook, Europe) was placed here. Because the small detachable balloon was inflated to its maximum capacity with contrast medium and not with liquid silicone monomers we decided to position a further microcoil immediately proximal to the detachable balloon. This was to prevent any possible recanalisation in the event of early deflation of the balloon. After this no filling of the fistula was seen (fig 2b). The left coronary artery and its branches were now seen much more clearly than before the embolisation procedure when there had been a "steal effect".

Immediately after the embolisation there was transient junctional rhythm, but no other ST segment changes. Isosorbide dinitrate (250 μg) was injected into the left coronary artery.

After the procedure, the serial electrocardiograms showed transient T wave inversion, which reverted to normal three days later. Serum creatine kinase peaked (325 U/l (normal <205 U/l)) 24 hours after the procedure and then returned to normal. A technetium pyrophosphate scan was normal two days after the procedure. There were no complications and the child made an uneventful recovery. A chest radiograph one day later showed that the balloon had deflated but was still in position. The murmur was not heard and no flow through the malformation was detected on Doppler echocardiography. At review two months later the patient was well and no murmur was heard. A chest radiograph showed the coils and balloon still in the same position.

Discussion

Primary congenital coronary fistulas to cardiac chambers or great vessels are rare. They are found in about one in every 500 patients having coronary arteriography.[5-7] They are the most common haemodynamically significant congenital coronary anomaly; in one series 21 fistulas were found in 34 cases.[8] Half of 363 coronary arteriovenous fistulas arose from the right coronary artery and 42% arose from the left coronary artery. Drainage was to any cardiac chamber but most commonly it was to the right ventricle (41%).[8]

As in our patient the condition most commonly presents as a murmur in a symptom free child.[7] Because complications in adult life can cause premature death the condition is usually treated surgically. Cardiac failure is the most common complication and increases with age.[7] Coronary ischaemia and angina can occur because of the steal effect of the fistula.[9] Though the resting electrocardiogram was normal in our patient, coronary arteriography showed the branches of the left coronary artery much better after the embolisation. Infective endocarditis[7 10] and atrial fibrillation can occur[10] and even rupture has been described.[11] As a result of these risks early prophylactic operation has been advocated.[7] Mortality from these operations in low, especially when the fistulas are on the inferior surface of the heart; even so the operation requires cardiopulmonary bypass with its consequent morbidity.

There are two specific technical requirements for embolisation of a coronary arteriovenous fistula. Firstly, the point of occlusion must be distal in the feeding artery and as close to the fistula as possible so that the risk of occluding normal coronary branches is low. These may not be so obvious due to the steal effect of a large fistula. Secondly, occlusion of a large high flow artery at a specific point is needed; this can be difficult and a detachable balloon is the ideal method. This allows immediate occlusion to be effected and is reversible if it is not satisfactory. In addition, it does not require more dangerous selective catheterisation of distal coronary branches with larger catheters.

The initial study in our patient showed that the coronary fistula was supplied by a single large septal branch. But an injection of contrast medium after embolisation also showed a much smaller second feeding branch. Had an operation been performed this second branch might easily have been missed. Embolisation methods have improved in recent years so that now even a small coronary artery branch such as this in a child can be selectively catheterised and occluded at the site of the fistula with a single microcoil. A latex balloon filled with contrast medium rather than silicone polymers was needed to occlude the large feeding branch. To prevent early deflation and recurrence of the fistula we placed a further coil proximal to the balloon. This coil alone would almost certainly not have produced occlusion.

When coronary arteriovenous fistulas are haemodynamically significant and a decision has been made to treat then embolisation should be considered the treatment of first choice. Modern embolisation techniques, which allow the use of more than one type of occlusive device, enable a precise intraoperative diagnosis and successful occlusion of fistulas—even those supplied by more than one artery.

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Balloon dilatation of tricuspid stenosis caused by carcinoid heart disease

P A Mullins, J A Hall, L M Shapiro

Abstract

Double balloon dilatation of tricuspid stenosis caused by carcinoid heart disease was successful in a woman of 77.

Case report

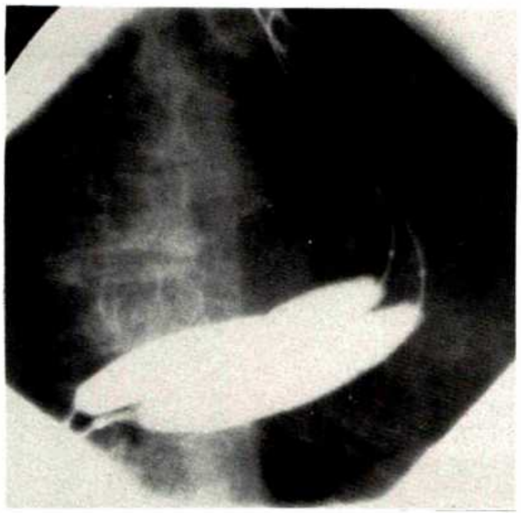
A 77 year old woman presented with a one year history of progressive dyspnoea with associated ankle oedema, weight loss, flushing attacks, and profuse recurrent diarrhoea.

On examination the pulse was regular and she was normotensive. Jugular venous pressure was elevated with a prominent systolic wave. There was a mid-diastolic murmur at the left sternal edge and a pansystolic murmur in the lower parasternal area; both were louder on inspiration. There was also pitting oedema up to the lower abdomen, pulsatile 4 cm hepatomegaly, and ascites.

The chest *x* ray showed cardiomegaly with upper lobe venous distension suggestive of pulmonary oedema. Haemoglobin, urea and electrolytes, liver function tests, and the electrocardiogram were within normal limits. Cross sectional echocardiography showed thickening and reduced excursion of the tricuspid valve. Doppler echocardiography showed a gradient of 10 mm Hg across the tricuspid valve and moderate tricuspid regurgitation. Liver ultrasound examination showed multiple echogenic areas throughout the liver parenchyma consistent with multiple metastases. Urinary 5-hydroxyindole acetic acid excretion was between 82–189 mg/24 h (normal < 14 mg/24 h). These findings confirmed the diagnosis of malignant carcinoid syndrome affecting the tricuspid valve.

Results of Doppler examination and catheter studies before and after dilatation

	Before dilatation	*After dilatation*
Right atrial pressure (mm Hg):		
"a" wave	24	24
"v" wave	44	36
Right ventricular pressure (mm Hg):		
Systolic	52	50
End diastolic	18	20
Tricuspid valve gradient (mean mm Hg)	10·5	7·6
Heart rate (beats/min)	75	75
Tricuspid valve area (cm²) (Doppler)	0·9	1·4



Two balloon catheters fully inflated across the tricuspid valve.

The patient was treated with somatostatin analogue and diuretics. We considered the tricuspid stenosis to be the most important abnormality. In view of her poor clinical condition and associated malignancy we attempted balloon dilatation of the tricuspid valve.

Two 7 French Gensini catheters were advanced through the right femoral vein, across the tricuspid valve, and lodged in the main pulmonary artery. They were replaced by two 0·038 inch exchange guide wires. Two balloon catheters (18 mm and 15 mm) were passed over the guide wires and fully inflated across the valve (figure). Doppler and direct catheter pressure measurements were obtained at regular intervals throughout the procedure (table).

The patient did well immediately after the procedure. There were reductions in dyspnoea and pulmonary and peripheral oedema. Follow up echocardiography up to a month after the procedure showed no increase in valve gradient or in the degree of tricuspid valve regurgitation.

Discussion

Carcinoid heart disease was originally described in 1954 by Thorson *et al.*[1] Over half the tumours arise initially in the appendix and the rest arise from the large intestine. When liver metastases occur hormonal factors including 5-hydroxytryptamine can produce direct cardiac effects.

Characteristically, the right sided cardiac valves are more commonly affected than the left sided valves. The ventricular aspects of the valve leaflets are affected by fibrous plaques. These consist of smooth muscle cells embedded in connective tissue, and endothelial thickening may occur. Clinically, pulmonary stenosis and tricuspid regurgitation

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are the commonest valve lesions although, as in this patient, tricuspid stenosis also occurs. The prognosis for patients with carcinoid heart disease is poor.[2] The most common cause of death is heart failure from valve disease.

Successful balloon dilatation of tricuspid valve stenosis of rheumatic origin[3] and of a stenosed bioprosthetic valve[4] have already been described.

We showed that balloon dilatation of tricuspid valve stenosis caused by carcinoid heart disease is a safe and effective treatment. The prognosis for these patients is poor and if palliative cardiac surgery can be avoided the patient's quality of life will be much improved. We believe that the results of balloon dilatation of pulmonary stenosis caused by carcinoid heart disease are likely to be as effective as dilatation of the tricuspid valve.

We thank Dr D Russell Hall for allowing us to report this case.

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Br Heart J 1990;**63**:251–2

Pulmonary artery sling: definitive diagnosis by colour Doppler flow mapping avoiding cardiac catheterisation

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Abstract

Pulmonary artery sling is a rare abnormality that usually presents in infancy with wheeze or stridor. Diagnoses by cross sectional echocardiography, computed tomography, and magnetic resonance imaging have been described but pulmonary arteriography was regarded as essential for a definite diagnosis. The use of colour Doppler adds to the diagnostic certainty of cross sectional echocardiography and colour Doppler provided a definite diagnosis in an infant that allowed surgical repair without the need for cardiac catheterisation. Postoperative flow through the left pulmonary artery was also assessed by Doppler, and this avoided the need for repeat catheterisation or perfusion lung scanning.

An aberrant left pulmonary artery or pulmonary artery sling usually presents in early infancy with signs of respiratory obstruction. In about 40% of cases it is associated with other cardiac abnormalities[1] but cardiac symptoms or signs are often not evident at presentation. The abnormality cannot be diagnosed clinically and the diagnosis rests on investigations.

The aberrant left pulmonary artery may be shown by cross sectional echocardiography,[2] computed tomography,[3] and magnetic resonance imaging.[4] None the less, pulmonary arteriography has been considered essential for confirmation of the diagnosis.[3-5] We report a patient in whom the diagnosis was confidently established by colour Doppler combined with cross sectional echocardiography and surgical repair was undertaken without cardiac catheterisation.

Case report

A 3 month old boy presented with intermittent wheeze and stridor. Clinical examination and *x* ray of the chest were normal. Barium swallow examination did not show any abnormalities. In view of the stridor, bronchoscopy was carried out and showed a posterior pulsatile indentation in the trachea that suggested a pulmonary sling. The infant was referred for a cardiac assessment at this stage and an echocardiogram was performed. Parasternal short axis and subxiphoid views showed that the main pulmonary artery did not bifurcate in the usual manner and showed a break in the continuity of the posterior wall of the right pulmonary artery with an echo free space leading from it (fig 1). Colour Doppler confirmed that the echo free space was an aberrant artery and not an artefact because it showed flow into the space from the right pulmonary artery (fig 2). The aortic arch was normal and there were no intracardiac abnormalities. On the basis of these findings, surgical repair was carried out with subsequent resolution of the respiratory symptoms. Colour Doppler flow mapping performed three months after operation showed unobstructed flow into the left pulmonary artery. The maximum velocity across the origin of the left pulmonary artery was only 1·9 m/s, confirming that there was no stenosis.

Discussion

Pulmonary artery sling is a rare cause of respiratory obstruction in early infancy. A barium swallow examination is often the initial diagnostic investigation carried out in infants presenting with significant stridor or wheeze and the classic anterior indentation of the oesophagus produced by the aberrant left pulmonary artery may be seen. On the other hand, the barium swallow may be normal in more than 20% of cases[1] and an anterior indentation may also be caused by a bronchial cyst, reduplication of the oesophagus, enlarged lymph nodes, and a rare form of aberrant right subclavian artery. Thus barium swallow examination cannot be relied upon as a definitive diagnostic test.

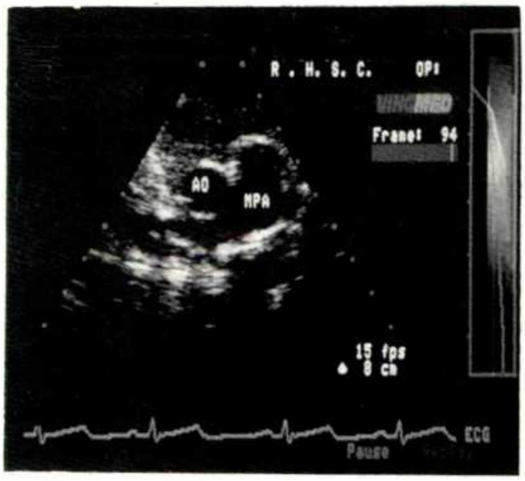

Figure 1 Parasternal short axis view showing absence of normal bifurcation of the main pulmonary artery. The aberrant origin of the left pulmonary artery is not conclusively shown. AO, aorta; MPA, main pulmonary artery.

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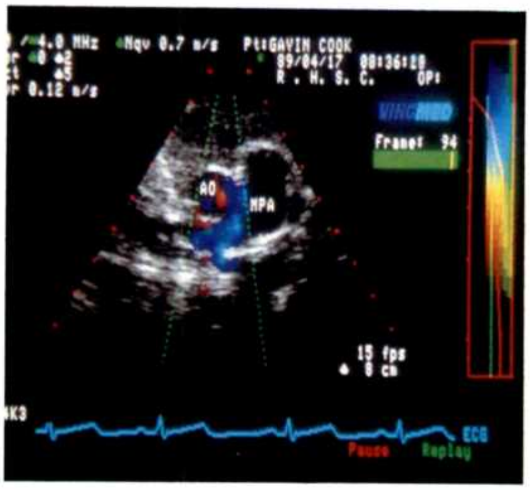

Figure 2 Same frame as fig 1 but with colour Doppler flow mapping showing flow from the right pulmonary artery into the aberrant vessel which courses posteriorly and leftwards. AO, aorta; MPA, main pulmonary artery.

Magnetic resonance imaging[4] and computed tomography[3] have been proposed as screening tests for a pulmonary sling but these techniques are not readily available, they require the infant to be motionless, which necessitates sedation, and further investigations are considered necessary to confirm the diagnosis and rule out associated cardiac malformations. Cross sectional echocardiographic findings in pulmonary artery sling were described by Yeager *et al* who commented that the anomalous artery may not be apparent on imaging in the presence of hyperinflation of the lungs, a finding that is not uncommon in this condition.[2] They suggested that cross sectional echocardiography was a useful screening test but believed that pulmonary arteriography was a more specific and sensitive investigation. In cases of pulmonary artery sling, bifurcation of the main pulmonary artery is not demonstrable on imaging and the aberrant vessel may be seen to arise from the proximal right pulmonary artery and run posteriorly and leftwards. Owing to the depth of imaging and overlapping of the lungs there may be some uncertainty as to whether the echo free space seen is an aberrant left pulmonary artery or an artefact caused by echo drop out. Since the initial posterior course of the anomalous pulmonary artery is in line with the Doppler transducer in the parasternal and subxiphoid short axis views, blood flow into it from the right pulmonary artery should be readily demonstrated by colour Doppler flow mapping. The aberrant origin of the left pulmonary artery from the proximal right pulmonary artery can thus be firmly established, avoiding the need for invasive cardiac catheterisation.

In view of the high incidence of postoperative occlusion of the left pulmonary artery it has been emphasised that follow up cardiac catheterisation is essential in all cases to evaluate flow through the left pulmonary artery.[6] This is no longer necessary because colour Doppler flow mapping provides an excellent means of assessing flow through the left pulmonary artery. If occlusion is present, reoperation is necessary to prevent the possible development of pulmonary hypertension.

Although a pulmonary sling or a vascular ring is an uncommon cause of stridor in infancy it is an important factor to consider because the infant may rapidly deteriorate and die before the diagnosis is made. Thus echocardiography with colour Doppler should be performed early in the assessment of all infants with appreciable stridor as it may show a vascular ring[7] or a pulmonary sling

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TECHNOLOGY

Short term results of percutaneous transluminal coronary angioplasty with the monorail technique: experience in the first 1000 patients

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Abstract

The monorail technique allows monitoring of all steps of the coronary angioplasty procedure by high quality coronary angiography; easy, rapid, and safe recrossing and redilatation of the lesion if necessary; and stepwise dilatation of a stenosis with sequential increase of size of balloons. Transstenotic pressure differences cannot, however, be measured through the narrow shaft of the standard monorail balloon catheter.

The monorail technique was used in 1014 patients (820 men, 194 women; mean age 57·8 years (range 24 to 84)). The indication for coronary angioplasty was stable angina in 52%, unstable angina in 40%, and acute myocardial infarction in 8%. Single vessel coronary angioplasty was attempted in 78%, multilesion coronary angioplasty in 11%, and multivessel coronary angioplasty in 11%. Angiographic success (reduction of stenosis to less than 50% of the luminal diameter) of all attempted lesions was achieved in 93%. The technique was clinically successful—that is, angiographic success of all attempted lesions, no occurrence of a major complication (death, myocardial infarction, acute bypass surgery), and improvement of symptoms—in 92% and partially successful in 1·3%. The clinical success rates were similar for stable angina (91%) and unstable angina (94%), but were somewhat lower for acute myocardial infarction (88%). Failure without major complication occurred in 3·4% of the patients. Failure with a major complication occurred in 3·3% (death 0·3%, myocardial infarction 2·4%, and acute bypass surgery 2·3%). The total major complication rate was higher in unstable angina (4·2%) than in stable angina (3·0%).

These results indicate that the monorail technique can be applied safely and effectively for coronary angioplasty of patients with stable angina, unstable angina, and acute myocardial infarction.

Significant advances have been made in the technology of guiding catheters, dilatation catheters, and guide wires since the first introduction of percutaneous transluminal coronary angioplasty in 1977 by Andreas Gruentzig.[1] Simpson *et al* further developed the balloon dilatation equipment by introducing a steerable coaxial guide wire.[2] Subsequent improvements were the miniaturisation of the balloon catheters (low profile balloons) to facilitate the crossing of very severe and distal stenoses. A more recent improvement is the combination of the long (exchange) guide wire technique[3 4] and a newly developed balloon catheter to form one new dilatation system: the monorail system, for which a change in dilatation technique is needed.[5] This monorail technique allows all steps of the coronary angioplasty procedure to be monitored on high quality angiograms: easy, rapid, and safe recrossing and redilatation of the stenosis if necessary; stepwise dilatation of a stenosis with sequential use of bigger balloons.

We describe our experience and the short term results of coronary angioplasty with the monorail technique in the first 1000 patients.

Patients and methods

PATIENTS

From June 1986 to December 1988 1472 patients underwent coronary angioplasty at the Thoraxcenter in Rotterdam. We excluded (*a*) patients in whom a stent was implanted (n = 13), (*b*) patients who were selected for the assessment of a newly developed catheter balloon system (n = 46); and (*c*) patients with bifurcation lesions in whom the (partial) kissing balloon technique was used (n = 15). Table 1 shows the baseline clinical characteristics of the remaining 1398 patients. These patients were classified into three groups: 1014 patients were selected for coronary angioplasty with the monorail technique, 325 patients were selected for coronary angioplasty with the long guide wire technique, and 59 patients were selected for coronary angioplasty with other balloon catheters (microbore, 54 patients; balloon on wire, five patients).

ANGIOGRAPHY

Coronary artery lesions were classified as occurring in the left anterior descending

Table 1 Baseline clinical characteristics of patients according to type of coronary angioplasty attempted

	Monorail technique (n=1014) % (n)	*Long guide wire technique (n=325) % (n)*	*Other technique* (n=59) % (n)*
Mean age (range) (yr)	58 (24–85)	57 (32–82)	56 (35–78)
> 70 yr	11 (108)	12 (39)	15 (9)
Females	19 (194)	16 (53)	22 (13)
Old MI	15 (147)	18 (57)	32 (19)
Previous CABG	10 (97)	14 (47)	14 (8)
EF < 45% (%)	5 (47)	5 (16)	7 (4)
Multivessel disease			
2 vessel	19 (193)	23 (74)	25 (15)
3 vessel	8 (85)	12 (38)	7 (4)
Total occlusion	7 (75)	14 (47)	27 (16)
Stable angina	52 (523)	70 (227)	80 (47)
Unstable angina	40 (407)	26 (85)	20 (12)
Acute MI	8 (84)	4 (13)	0 (0)
Attempt per vessel.			
LAD	51 (578)	43 (159)	43 (32)
RCA	26 (291)	26 (96)	33 (26)
CX	20 (221)	25 (92)	23 (18)
Bypass graft	3 (36)	5 (17)	1 (1)
Left main stem	1 (5)	1 (2)	0 (0)
Attempts per patient:			
Single vessel	78 (791)	75 (244)	66 (39)
Multilesion	11 (114)	11 (36)	20 (12)
Multivessel	11 (109)	14 (45)	14 (8)

*Attempted coronary angioplasty with other standard dilatation technique and other balloons.
MI, myocardial infarction; CABG, coronary artery bypass grafting; EF, ejection fraction; LAD, left anterior descending artery; RCA, right coronary artery, CX, circumflex coronary artery, n = number of patients.

artery, left circumflex artery, and right coronary artery, whether or not they occurred within the artery itself or in a side branch of that artery. There was a separate category for lesions of bypass grafts or of the left main stem. Coronary stenosis was expressed as a percentage of the luminal diameter and a lesion of >50% was regarded as haemodynamically important. Multivessel disease was defined as a luminal arterial diameter narrowing of more than 50% in at least two major coronary arteries. A vessel was considered to be totally occluded when no anterograde flow of dye was visible at angiography immediately before the attempted coronary angioplasty. The ejection fraction was calculated from the left ventriculogram in the 30° right anterior oblique projection.

HISTORY

Unstable angina was defined as chest pain at rest associated with documented changes in the ST segment or T wave and no obvious signs of myocardial cell necrosis (an increase in cardiac enzymes of less than twice normal or no development of abnormal Q waves). Patients were considered for immediate coronary angioplasty if they had symptoms of acute myocardial infarction (severe, prolonged chest pain not relieved by glyceryl trinitrate and ST segment elevation of at least 1 mm in at least two contiguous leads) for less than 6 hours after the onset of symptoms.

CORONARY ANGIOPLASTY PROCEDURE

Intravenous heparin (100 mg) and aspirin (250 mg) were given at the start of the procedure. The electrocardiogram and blood pressure were monitored continuously. To prevent coronary spasm intracoronary isosorbide dinitrate (10 to 30 μg) was injected and this was repeated when necessary. The initial pressure of balloon inflation was 2·0 atms, with subsequent inflations of up to 12 atms. The duration of inflation was adjusted for electrocardiographic changes, the drop in blood pressure, or induced pain. The number of balloon inflations varied according to the appearance of the lesion on angiography immediately after dilatation.

Multivessel dilatation was defined as dilatation of one or more lesions in two or more major epicardial coronary arteries. Multilesion dilatation was defined as dilatation of two or more lesions in one major epicardial coronary artery. In patients with stable angina and multivessel angioplasty, dilatation of the most severe narrowing in the vessel supplying the largest amount of jeopardised myocardium (critical stenosis) was always attempted first and, if successful, additional vessel(s) were dilated. Angioplasty of a second or third vessel was not attempted if the attempted dilatation of the critical lesion was unsuccessful or when angiographic success was equivocal or if the result was consistent with a dissection that might progress to total occlusion. When a vessel with high grade disease supplied collaterals to another vessel, the vessel receiving the collateral supply was dilated first to protect collateral flow. When sequential lesions were present in one vessel, the more proximal lesion was dilated first. In patients with unstable angina and multivessel disease only the critical lesion (determined by the electrocardiographic changes and angiographic appearance—that is, the severity and complexity of the lesion, irregular borders, intracoronary thrombus) was dilated except in 37 patients who were judged to have more than one severe lesion. These were dilated in the same session. In patients with acute myocardial infarction only the infarct related lesion was dilated.

The success of the procedure was judged by both angiographic and clinical criteria. Angiographic success was defined as a reduction of the luminal diameter stenosis to < 50%. A complete clinical success was defined as angiographic success in all attempted lesions, associated with an improvement of symptoms and without evidence of myocardial infarction or the requirement for coronary artery bypass surgery during hospital stay. An incomplete clinical success was defined as angiographic success with the critical lesion but failure with additional lesion(s), associated with an improvement of symptoms and without evidence of myocardial infarction or need for coronary artery bypass surgery during hospital stay.

A coronary angioplasty was regarded as a failure if (*a*) the angiographer was unable to reach, cross, or dilate the critical lesion while

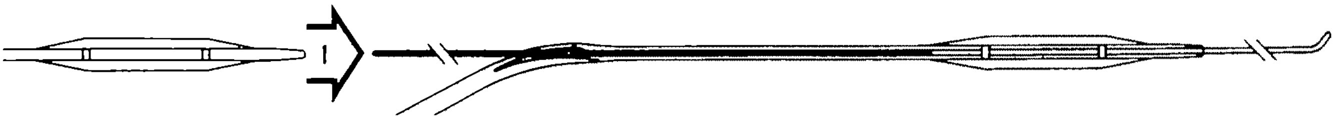

Figure 1 The monorail balloon catheter consists of a lumen running the length of the catheter to inflate and deflate the balloon, and a second lumen (1) limited to the distal end of the catheter that acts as a "monorail" and is occupied by the guide wire.

attempting to perform a coronary angioplasty (failure without complications) or (*b*) the coronary angioplasty procedure resulted in death, myocardial infarction, or emergency coronary artery bypass surgery. A peri-interventional (complication of angioplasty) myocardial infarction was defined as the development of an abnormal Q wave ($\geqslant$0·03 mm) or a typical increase in cardiac enzymes. A perioperative (complication of a bypass operation) myocardial infarction was defined as the development of an abnormal Q wave ($\geqslant$0·03 mm). All procedures were carried out with a surgical team on standby. After the procedure the sheaths were left in place for 6–8 hours and all patients were monitored for 24 hours in an intermediate coronary care unit. All patients were treated with oral nifedipine 60 mg daily for 24–36 hours after coronary angioplasty and were discharged after 1 to 2 days. The patients were treated with aspirin 500 mg daily for 6 months.

MONORAIL TECHNIQUE

The monorail balloon catheter (Bonzel-Schneider-Medintag) has a single lumen for balloon inflation and a second lumen limited to the first few centimetres of the distal end of the catheter. This second lumen is occupied by the guide wire that acts as a sliding rail (monorail) for the balloon catheter (fig 1). Table 2 shows the technical details for different types of monorail balloon catheters. In the monorail technique the guide wire alone (Schneider-Medintag 175 cm, 0·0012–0·0014 inch; ACS 175 cm, 0·0014 inch) is initially positioned across the lesion. The small diameter guide wire does not obstruct injection of contrast; thus it allows good delineation of the coronary anatomy and facilitates positioning of the wire across the lesion (fig 2a and b).

The distal lumen of the balloon catheter is then threaded over the positioned guide wire (the proximal part guide wire is outside the guiding catheter) and the catheter is advanced through the guiding catheter, into the coronary artery tree, and eventually across the lesion (fig 1). Because the position of the guide wire outside the patient is fixed most of the positioning and withdrawing of the balloon is performed without the need for fluoroscopic control and to and fro motion of the wire in the distal coronary vessel is prevented. The reduced shaft diameter of the balloon catheter means that the injection of contrast when the balloon is in the guiding catheter is not obstructed and this improves the delineation of the coronary anatomy (fig 2c and 3).

After the final dilatation of the lesion the balloon catheter is completely withdrawn outside the guiding catheter while the guide wire remains in the distal vessel. The result of dilatation can again be evaluated under high quality angiographic control and, when necessary, the lesion can be easily recrossed and redilated (fig 2d).

OTHER CORONARY ANGIOPLASTY TECHNIQUES

In the remaining patients in whom the monorail technique was not used, coronary angioplasty was performed by standard techniques with either fixed tip or steerable catheter systems or by the long guide wire technique.[3]

CLASSIFICATION OF PATIENTS

Monorail group

Patients were classified as being in the monorail group if the monorail technique was selected as the first choice of catheter balloon system to be used. The patients always remained in the monorail group if, after failure with the monorail technique, an attempt with another balloon catheter system was successful or unsuccessful.

Long guide wire group and other technique group

Patients were classified as being in the long guide wire group or other technique group if either technique was selected as the first approach. The patients remained in this group even after crossover to another technique.

Results

Most of the baseline clinical characteristics were similar in the three groups (table 1). However, attempted coronary angioplasty of a total occluded lesion and multilesion dilatation were more common in the long guide wire and the other technique groups.

Table 3 shows the short term results of coronary angioplasty with the different techniques. The overall clinical and angiographic success rate was lower in the groups classified as long guide wire technique and in particular in those classified as the other technique group but this may have been because more total occlusions were attempted. The differences in outcome therefore are a reflection of patient selection and do not indicate that one technique was better than the other.

Table 4 shows the results of attempts with

Table 2 Technical details of different monorail dilatation catheters

	Balloon diameter (mm)	*Deflated balloon profile (inch)*	*Shaft diameter*	*Maximum recommended balloon pressure (atm)*
Monorail-Bonzel, PVC (super)-low profile	2·0–4·2	0·043–0·061	3F	8–10
Monorail Piccolino, PET material	1·5–4·25	0·028–0·040	3F	8–12
Monorail-Bonzel Snake, with distal pressure measurement, PVC	3·0–4·2	0·058–0·063	3·6F	8

All three catheters are of the Schneider-Shiley type.
PCV, polyvinylchloride; PET, polyethylene.

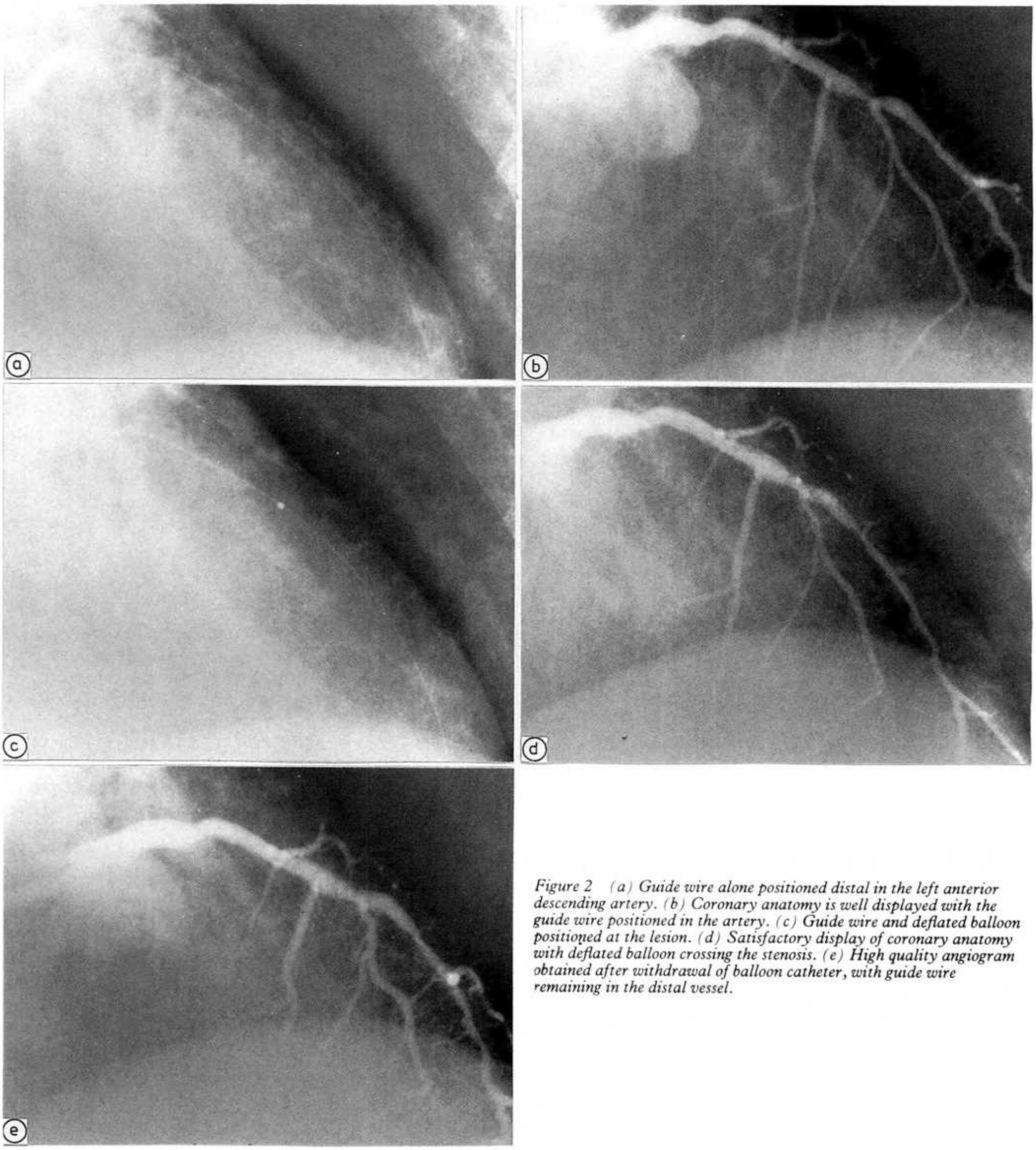

Figure 2 (a) Guide wire alone positioned distal in the left anterior descending artery. (b) Coronary anatomy is well displayed with the guide wire positioned in the artery. (c) Guide wire and deflated balloon positioned at the lesion. (d) Satisfactory display of coronary anatomy with deflated balloon crossing the stenosis. (e) High quality angiogram obtained after withdrawal of balloon catheter, with guide wire remaining in the distal vessel.

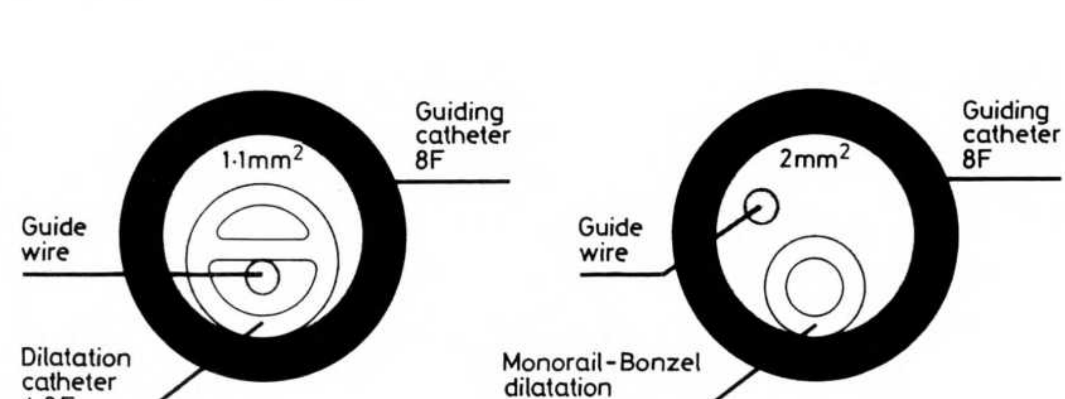

Figure 3 Comparison of space available within 8F guiding catheter when a conventional dilatation catheter (1·1 mm²) or a monorail balloon catheter (2 mm²) is used.

Table 3 Short term results of coronary angioplasty with the monorail technique, the long guide wire technique, and other technique

	Monorail technique (1014)	*Long guide wire technique (325)*	*Other technique (59)*
Clinical success (%) (nos of patients)			
Complete	92 (933)	87 (282)	66 (39)
Partial	1·3 (14)	2·5 (8)	8·5 (5)
Total of attempted lesions (no)	1240	407	79
Angiographic success all lesions (%)*	93 (1154)	88 (359)	73 (58)
Total of attempted total occlusions	75	47	16
Angiographic success total occlusions (%)*	60 (45)	49 (23)	25 (4)
Angiographic success (total occlusions excluded) (%)	95 (1109)	93 (336)	86 (54)
Failure without complication (%)†			
Total	3·4 (34)	6·0 (20)	22 (13)
Inability to cross with wire	1·8 (18)	4·5 (14)	20 (12)
Inability to cross with balloon	0·4 (4)	1·0 (4)	2 (1)
Inability to dilate	1·2 (12)	0·5 (2)	0 (0)
Failure with major complication (%)†			
Total	3·3 (33)	4·5 (15)	3·5 (3)
Death	0·3 (3)	0·6 (2)	0 (1)
Myocardial infarction	2·4 (24)	2·8 (9)	3·5 (2)
Acute bypass surgery	2·3 (23)	3·4 (11)	2 (1)
Other complications (%)†:			
Clot on wire	1·4 (14)	2 (7)	2 (1)
Spasm	1·2 (12)	1·8 (6)	2 (1)
Ventricular fibrillation	0·7 (7)	0·6 (2)	0 (0)
Side branch occlusion	0·8 (8)	0·6 (2)	0 (0)

*Number of lesions is given in parentheses.
†Number of patients is given in parentheses.

another technique or balloon catheter after initial failure with the monorail technique. Tables 5, 6, and 7 show the short term results of percutaneous transluminal coronary angioplasty with use of the monorail technique in patients with stable angina, unstable angina, and acute myocardial infarction. These results indicate that the monorail technique can be used as an elective (table 5), semi-elective (table 6), or emergency procedure (table 7) and indicate that with the use of the monorail technique stenoses in all three major coronary arteries and venous bypass grafts are equally accessible and that the primary success rates and reasons for failure in these vessels are comparable. Table 8 shows the short term results of attempted coronary angioplasty with the monorail technique for totally occluded lesions. The higher success rate in patients with unstable angina reflects the shorter interval between total occlusion and attempted coronary angioplasty.

Table 4 Short term results of attempts with another balloon dilatation catheter after initial failure with the monorail technique

Attempted lesions	*Attempt with other balloon catheter* *Total (n)*	*Success (n)*	*Failure (n)*
Single lesion	5	1 (0)	4 (2)
Multilesion/multivessel			
Culprit lesion	3	3 (1)	0 (0)
Additional lesion(s)	8	7 (2)	1 (1)

Numbers in parentheses are patients with total occlusion.

Discussion

Primary success of percutaneous transluminal coronary angioplasty depends on many factors. The most important are patient selection, lesion location, operator experience, dilatation equipment, and adequate radiographic equipment.[6-9] Undoubtedly improvements in balloon catheter designs and dilatation techniques have increased success rates. We describe the initial results obtained with the use of the monorail technique and do not compare the success rates or complication rates with the monorail technique with other techniques or other balloon catheter systems. Although such a study is desirable, it would require a randomised design and, because of the expected small differences in outcome, it would require the recruitment of a large study group from more than one centre with many investigators. Furthermore, such a study would take several years and continuing refinements and improvements of balloon catheters or the introduction of new techniques (laser, atherectomy, abrasive catheters, ultrasound energy) would make the comparison unreliable. We describe our experience with the monorail technique used as a primary routine in one interventional cardiology centre in which about

Table 5 Short term results of percutaneous transluminal coronary angioplasty by the monorail technique in patients with stable angina

		Clinical success			*Failure**					
					No complications		*With complications*			
	Total (n)	*Angiographic success % (lesions)*	*Complete % (n)*	*Partial % (n)*	*UC % (n)*	*UB % (n)*	*Total % (n)*	*Death (n)*	*MI (n)*	*CABG (n)*
Single vessel attempt:										
LAD	202	92 (186)	92 (186)	—	2·5 (5)	1·5 (3)	4·0 (8)	0	4	8
RCA	99	87 (86)	87 (86)	—	6 (6)	2 (2)	5 (5)	0	3	2
CX	70	94 (66)	94 (66)	—	3 (2)	1·5 (1)	1·5 (1)	0	1	1
Bypass graft	9	89 (8)	89 (8)	—	11 (1)	0	0	0	0	0
Left mainstem	4	100 (4)	100 (4)	—	0	0	0	0	0	0
Multilesion attempt:										
LAD	41	96 (80)	95 (39)	2·5 (1)	0	0	2·5 (1)	0	1	1
RCA	22	98 (42)	95 (21)	5 (1)	0	0	0	0	0	0
CX	4	88 (7)	75 (3)	25 (1)	0	0	0	0	0	0
Multivessel attempt:										
LAD/CX	31	97 (58)	94 (29)	6 (2)	0	0	0	0	0	
LAD/RCA	23	93 (43)	91 (21)	4 (1)	0	0	4 (1)	0	1	0
RCA/CX	12	75 (18)	58 (7)	33 (4)	8 (1)	0	0	0	0	0
Bypass graft/other	4	100 (8)	100 (4)	0 (0)	0	0	0	0	0	
LAD/CX/RCA	2	83 (5)	50 (1)	50 (1)	0	0	0	0	0	0
All attempts	523	92 (611)	91 (475)	2 (11)	2·8 (15)	1·2 (6)	3·0 (16)	0	10	12

*UC, uncrossed wire; UB, unable to cross lesion to dilate with balloon.
MI, myocardial infarction; CABG, coronary artery bypass grafting; LAD, left anterior descending coronary artery; RCA, right coronary artery, CX, circumflex coronary artery n = number of patients.

Table 6 Short term results of percutaneous transluminal coronary angioplasty by the monorail technique in patients with unstable angina

		Clinical success			*Failure**					
					No complications		*With complications*			
	Total (n)	*Angiographic success % (lesions)*	*Complete % (n)*	*Partial % (n)*	*UC % (n)*	*UB % (n)*	*Total % (n)*	*Death (n)*	*MI (n)*	*CABG (n)*
Single vessel attempt:										
LAD	183	94 (172)	94 (172)	—	1 (2)	0	5 (9)	2	7	6
RCA	69	93 (64)	93 (64)	—	1·5 (1)	0	6 (4)	1	3	2
CX	62	97 (60)	97 (60)	—	0	0	3 (2)	0	2	2
Bypass	9	100 (9)	100 (9)	—	0	0	0 (0)	0	0	0
Multilesion attempt.										
LAD	26	94 (50)	88 (23)	4 (1)	0	0	8 (2)	0	2	1
RCA	12	100 (24)	100 (12)	—	0	0	0 (0)	0	0	0
CX	9	94 (17)	89 (8)	11 (1)	0	0	0 (0)	0	0	0
Multivessel attempt:										
LAD/CX	13	96 (25)	92 (12)	8 (1)	0	0	0	0	0	0
LAD/RCA	12	100 (24)	100 (12)	—	0	0	0	0	0	0
RCA/CX	8	100 (16)	100 (8)	—	0	0	0	0	0	0
L-main/CX	1	100 (2)	100 (1)	—	0	0	0	0	0	0
Bypass/LAD(2) CX(1)	3	100 (6)	100 (3)	—	0	0	0	0	0	0
All attempts	407	95 (469)	94 (384)	0·7 (3)	0 7 (3)	0	4·2 (17)	3	14	11

n = number of patients.
See footnote to table 5 for abbreviations.

*Table 7 Acute results of percutaneous transluminal coronary angioplasty by the monorail technique in patients with acute myocardial infarction**

			Failure	
	n	*Clinical success (%) (n)*	*UC % (n)*	*UB % (n)*
Single vessel:				
LAD	43	93 (40)	0	7 (3)
RCA	32	81 (26)	0	19 (6)
CX	8	88 (7)	0	12 (1)
Bypass graft	1	100 (1)	0	0
All attempts	84	88 (74)	0	12 (10)

*There were no deaths.
See footnote to table 5 for abbreviations.

500 patients per year were treated by angioplasty.

MONORAIL TECHNIQUE

Nowadays, in elective procedures with low profile or super low profile dilatation catheters the initial success rate should be well over 90%.[10–12] None the less, angioplasty patients continue to be at risk of major periprocedural complications. Optimal visualisation and continued access to the distal part of the vessel are useful in preventing, recognising and facilitating the management of these acute complications.

The monorail technique allows (*a*) optimal visualisation to monitor all the important steps of the coronary angioplasty procedure; (*b*) safe, rapid, and easy recrossing of the lesion if necessary, and (*c*) initial crossing of a tight or complex lesion with a small balloon and recrossing of the stenosis with larger balloons. Optimal visualisation is essential for negotiation of the proximal and distal parts of the coronary artery, for crossing of the lesion, and for recognition and management of the complications of the procedure. If dilatation is incomplete or an acute coronary occlusion occurs during angioplasty the monorail technique enhances recognition of these situations and allows easy and safe recrossing with the same or a larger balloon. If this is unsuccessful a monorail coronary perfusion catheter can be introduced and coronary blood perfusion can be performed. The guide wire is withdrawn only after the control angiogram has shown a satisfactory result. In patients with a high risk of abrupt occlusion after an initial successful dilatation the technique permits monitoring of the patient in the catheterisation laboratory with continued access provided by the wire in the distal part of the vessel.

LIMITATIONS OF THE MONORAIL TECHNIQUE

The shaft of the standard monorail balloon catheter is too narrow to allow measurement of the transstenotic pressure difference. Undoubtedly measurement of transstenotic pressure differences by commercial equipment is less accurate than by high-fidelity micro-

Table 8 Short term results of percutaneous transluminal coronary angioplasty by the monorail technique in patients with occlusion of a coronary artery

				Failure					
		Clinical success		*No complications*		*With complications*			
	(n)	*Complete % (n)*	*Partial % (n)*	*UC % (n)*	*UB % (n)*	*Total % (n)*	*Death (n)*	*MI (n)*	*CABG (n)*
Stable angina	50	52 (26)	8 (4)	30 (15)	8 (4)	2 (1)	0	1	0
Unstable angina	25	76 (19)	0 (0)	12 (3)	0 (0)	12 (3)	1	2	2

See footnote to table 5 for abbreviations.

manometers.[13 14] None the less, haemodynamic evaluation of the lesion by such methods may help to predict restenosis[15] and provide immediate additional information to support the angiographic result. Reduction in the diameter of the catheter allows high quality visualisation but precludes measurement of the transstenotic pressure gradient whereas an increase in diameter allows measurement of a pressure gradient but precludes high quality angiography. We believe that high quality visualisation is more helpful than measurement of a transstenotic pressure drop in the assessment of the result immediately after dilatation. The Monorail–Bonzel Snake balloon catheter, however, is designed to measure the drop in pressure gradient (table 2).

The poor pushability and occasional kinking of the guide wire during retraction of the balloon with the first generation monorail catheters caused some concern. Both problems have been substantially improved by lengthening of the second distal lumen, which accommodates the guide wire, from 5 cm to 9–17 cm (Monorail Snake, 9 cm; Picolino, 17 cm).

The risk of thromboembolic complications (1·4%) was higher because the guide wire remains in the coronary artery for longer. Full anticoagulation must be maintained (a second or third bolus infusion of heparin may be needed during lengthy procedures) with on line monitoring of anticoagulation.

CONCLUSION

With the monorail technique it is easier to obtain good angiograms to monitor all important steps of the coronary angioplasty procedure and safe, easy, and rapid recrossing is facilitated. The monorail technique was successful in 90% of 1000 patients and the rate of major complications (death, myocardial infarction, acute bypass surgery) was <4%. The transstenotic pressure difference cannot be measured through standard monorail balloon catheters. In future, however, smaller guide wires will be developed to allow measurement of pressure through the monorail catheter.

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Br Heart J 1990;63:260–1

TECHNOLOGY

A technique for replacing a prosthetic aortic valve after total aortic root replacement

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Abstract

The excision and replacement of a failed aortic valve bioprosthesis in a composite tubular graft in two patients with Marfan syndrome was accomplished without replacing the composite graft.

A composite tubular graft with mechanical valve prosthesis can be used to replace the ascending aorta and aortic valve in cases of Marfan syndrome.[1] Some surgeons prefer to use a xenograft valve prosthesis in the composite graft. Although xenograft protheses are less likely to cause thromboembolic complications they fail more quickly and need to be replaced. We describe the use of technique for replacing a xenograft valve within such a composite graft without having to re-do cardiac, aortic, or coronary anastomoses in two patients.

Case reports

CASE 1

A 39 year old man with Marfan syndrome presented to our unit with increasing breathlessness. Eleven years previously he had undergone mitral valve replacement with a 33 mm Carpentier-Edwards bioprosthesis. Four years later he underwent composite aortic root replacement with reimplantation of the coronary arteries with a 30 mm woven Dacron graft to which a 25 mm Carpentier-Edwards prothesis was sewn. On admission to our unit investigation showed severe aortic regurgitation. At operation full cardiopulmonary bypass was established with pump return to the right femoral artery. The patient was core cooled to 25°C. The aortic graft was cross clamped and opened obliquely. Cold St Thomas's cardioplegia mixture was infused into the coronary ostia and topical cooling was added. The failed aortic bioprothesis had severe calcification with leaflet tears and was freely incompetent. The stent part of the valve was excised leaving the sewing ring behind (fig 1) and the proximal graft suture line intact. A 23 mm St Jude aortic prothesis was inserted with interrupted 2/0 Ethibond sutures. The procedure was completed uneventfully. He was discharged on the 10th postoperative day and remains well with normal aortic and mitral valve function a year later.

CASE 2

A 36 year old woman with Marfan syndrome had undergone composite root replacement with reimplantation of the coronary arteries at another hospital six years before. A 27 mm Carpentier-Edwards valve had been sewn into a 30 mm Dacron conduit. She was admitted to a district hospital with breathlessness and signs of heart failure one month before operation. Then she was transferred to our hospital. She had pronounced oedema. Cardiac catheterisation indicated aortic regurgitation and stenosis and mild mitral regurgitation—all judged to be functional. Her coagulation fac-

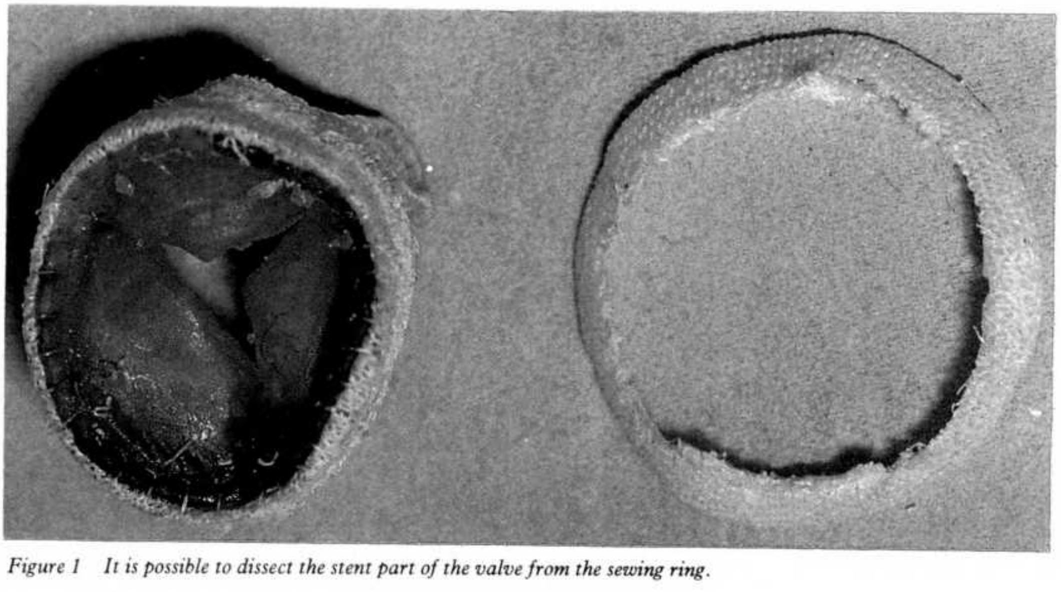

Figure 1 It is possible to dissect the stent part of the valve from the sewing ring.

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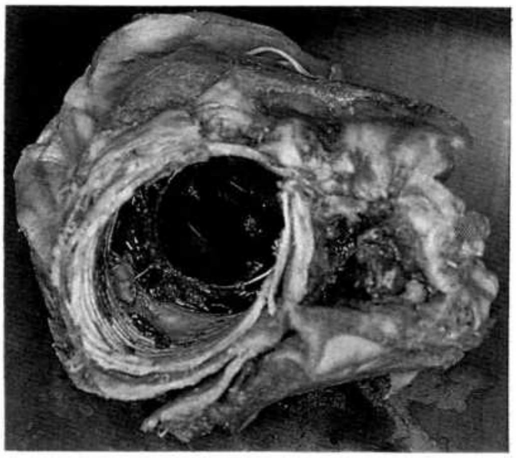

Figure 2 A St Jude valve in place after excision of the failed bioprothesis in patient 2.

tors and electrolyte concentrations were grossly abnormal. At emergency operation she had the 27 mm aortic bioprothesis removed and a 23 mm St Jude valve inserted in exactly the same way as the first patient (fig 2). Again the bioprothesis was severely calcified and had leaflet tears. Although the ischaemic time was less than 60 minutes cardiac output was low after operation and she died 48 hours later. Necropsy showed that the operation had been successfully accomplished; the mitral annulus was dilated and the myocardium was fibrotic. It was likely that death was caused by a combination of mitral regurgitation, which was more severe than we had assessed, and myocardial failure.

Discussion

The argument for using a bioprothesis in a composite root is essentially the same as for simple valve replacement. Many patients who undergo aortic root replacement, however, have Marfan syndrome and are liable to have cardiovascular problems at other sites. Anticoagulation is a significant disadvantage in such patients. Unfortunately patients are generally young and standard bioprotheses tend to degenerate more rapidly in them than in older patients. The choice of valve for individual cases is thus difficult. We showed that the excision and replacement of a failed bioprothesis in a composite root is not technically difficult and that it is unnecessary to replace the whole composite graft.

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LETTER TO THE EDITOR

Staffing in cardiology in the United Kingdom 1988: Fifth biennial survey

SIR,—Our data (1989;**62**:482–7) for the number of cardiologists in Scotland that were published in our fifth biennial survey have been criticised. We have reviewed them, and, using the definition given in the paper, we accept that 14 physicians who should have been included were indeed omitted. We regret this misunderstanding which arose principally because of a difference in the designation of training posts in Scotland compared with that in England and Wales.

The errors affected tables 3 and 9 which are republished here with appropriate corrections.

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Table 3 *Number of cardiologists (cardiovascular physicians) in Scotland by health board at 1 July 1988*

		Cardiology only		*Major interest*		
Health board	*Population (1987)*	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Total*
Argyll and Clyde	443 128	0	0	1	0	1
Ayrshire and Arran	374 752	0	0	2	0	2
Borders	102 141	0	0	0	0	0
Dumfries and Galloway	147 036	0	0	0	0	0
Fife	344 590	0	0	0	0	0
Forth Valley	272 077	0	0	0	0	0
Grampian	502 863	3	0	0	0	3
Greater Glasgow	951 219	11	3	7	0	21
Highland	200 608	0	0	1	0	1
Lanark	563 448	0	0	3	0	3
Lothian	743 700	6	2	1	0	9
Orkney	19 338	0	0	0	0	0
Shetlands	22 429	0	0	0	0	0
Tayside	393 762	2	0	0	0	2
Western Isles	31 048	0	0	0	0	0
Totals	5 112 139	22	5	15	0	42

Table 9 *Scottish health boards without cardiovascular physicians at 1 July 1988*

Health board	*Pop without (mid 1987 estimate)*
Borders	102 141
Dumfries and Galloway	147 036
Fife	344 590
Forth Valley	272 077
Orkney	19 338
Shetlands	22 429
Western Isles	31 048
Total for the 7 boards	938 659

NOTICE

British Cardiac Society
The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts was 19 January 1990.

Br Heart J 1990;63:263-4

BRITISH
HEART
JOURNAL

Editorial

Hypertrophic cardiomyopathy: one disease or several?

The first clinical or pathological descriptions of a disease are inevitably biased by patient selection. With time the range of features encompassed by the disease widens inevitably leading to a consideration of where the actual limits lie—some wish to "split" others to "lump". Hypertrophic cardiomyopathy has reached this stage and it is now uncertain whether there is one genetic abnormality with protean manifestations or several genetic abnormalities, all of which produce morphological and clinical features of abnormal ventricular hypertrophy.

Teare provided the first unequivocal illustration of the morphological features of what is now known as hypertrophic cardiomyopathy.[1] His paper is the most cited paper from the *British Heart Journal*: it has been quoted more than 390 times.[2] His method of dissecting the heart was unorthodox but had the advantage of clearly displaying the anatomy of the left ventricular outflow tract. Thus he was able to recognise that there was an association between asymmetrical hypertrophy of the interventricular septum, bulging out beneath the aortic valve, and sudden unexpected death in young individuals. Coincidental with this morphological description there was growing recognition of subaortic stenosis in living individuals, and it was not difficult to see that the pathological features described by Teare were the likely basis for this.

Teare also described the characteristic histological appearances of bundles of myocytes running in several directions and separated by connective tissue. The presence of a typical specimen of asymmetrical septal hypertrophy, misclassified as a rhabdomyoma of the heart in St George's Medical School museum, biased him towards the idea of a localised benign tumour and he therefore did not appreciate that the biological changes represented a generalised abnormality of heart muscle.

During the 1970s it became recognised that the disease was not as circumscribed in its clinical features as the name asymmetrical septal hypertrophy implied. Echocardiographic surveys showed that while the upper septum and anterior wall of the left ventricle was the most common site of hypertrophy the segment of abnormal muscle may lie in the mid-septal, lateral, posterior, or apical regions of the left ventricle[3 4] or in the right ventricle.[5] Symmetrical involvement of the left ventricle is another recognised variant.[6] Family studies show that the expression of the disease within a family is very variable.[7] Teare later recognised that the morphological features of the disease were more varied than his initial description of asymmetrical septal hypertrophy and that it occurred in elderly people dying of other causes.[8] The early descriptions of the disease emphasised the high risk of both sudden death and cardiac failure, but later surveys pointed out that the disease can be relatively benign and compatible with a long asymptomatic phase.[7 9] Anatomical criteria have now been used to create a broader definition of hypertrophic cardiomyopathy as a hypertrophied, non-dilated, left ventricle in the absence of a cardiac or systemic disease that itself could produce left ventricular hypertrophy.[10]

Ideally there should be a single "gold standard" for the disease—the histological features seem to be an obvious candidate. One characteristic of hypertrophic cardiomyopathy, unlike hypertrophy secondary to an increased volume or pressure load, is the very uneven increase in myocyte size and nuclear ploidy. Another characteristic, the myocyte disorganisation or disarray first recognised by Teare, has a variety of forms. Myofibrillar disorganisation is an intracellular abnormality of contractile filament organisation, and its specifity is low because it is also found in a wide range of cardiomyopathies. True disarray is a malarrangement of cell to cell contact—the shape of individual myocytes is abnormal and lateral attachments are increased. The histological pictures are complex and depend on the plane in which the cells are sectioned.[11] The most common form consists of areas of myocardium in which adjacent cardiac muscle cells are aligned obliquely, producing a whorled, tangled, or pinwheel configuration. This histological appearance, however, is not absolutely specific because it is also found in focal areas in normal hearts as well as in hearts in which valve disease has resulted in hypertrophy.[12] The junction of the right ventricular free wall and the septum is especially likely to have focal areas of disarray. But the extent of disarray has a high specificity and sensitivity for hypertrophic cardiomyopathy. Maron and Roberts used a planimetric method to measure the percentage area of the septum occupied by disarray in 54 patients with a firm clinical and echocardiographic diagnosis of hypertrophic cardiomyopathy.[11 13] They used 144 hearts from normal individuals or from those with hypertrophy caused by aortic valve disease, hypertension, and congenital heart disease for comparison. The mean (SEM) percentage area of septum containing disarray was 31 (3)% in hypertrophic cardiomyopathy and 1·5 (0·6)% in controls. Whereas a cut off point of 5% gives a 86% sensitivity and 90% specificity for disarray being diagnostic of hypertrophic cardiomyopathy, six patients with all the other hallmarks of hypertrophic cardiomyopathy had less than 5% disarray and three of these had no disarray at all.

Two control hearts showed more than 20% disarray. As a corollary to this demonstration of the variable amount and uneven distribution of disarray in whole hearts, biopsy in life can neither confirm nor refute the diagnosis of hypertrophic cardiomyopathy. The chance of obtaining false negative findings is high because of sampling error; false positives arise because the biopsy specimen can include a focal area of disarray in a heart without hypertrophic cardiomyopathy. This does not mean that the use of a scoring system based on a constellation of abnormal histological findings in a biopsy specimen including the myocyte size, nuclear size, and myocyte disorganisation cannot distinguish between hypertrophic cardiomyopathy and normal hearts[14] but only that biopsy will not resolve a doubtful clinical diagnosis.

The number of myocytes in a transect of the septum was higher in hypertrophic cardiomyopathy than when an equivalent degree of hypertrophy was attributable to a known cause such as hypertension.[15-17] Such results indicate that in hypertrophic cardiomyopathy there is an increase in the total number of myocytes (hyperplasia) as well as an increase in myocyte size (hypertrophy). It is not known whether this hyperplasia occurs in utero, in early childhood, or in the adolescent growth phase. Sequential echocardiographic study throughout life in individuals from families with hypertrophic cardiomyopathy suggests that segments of hypertrophic myocardium are first detected in the adolescent growth phase and do not subsequently spread out into the rest of the ventricle.[18]

Two papers in this issue of the *British Heart Journal* propose a further widening of the clinical spectrum of hypertrophic cardiomyopathy. Maron *et al* (p 308) describe a young man, from a family known to have hypertrophic cardiomyopathy, who dropped dead: necropsy showed a macroscopically normal heart of normal weight and no hypertrophy.[19] Histological examination, however, showed extensive myocardial disarray. The implication is that had the patient not died the typical echocardiographic abnormality of segmental hypertrophy would have appeared later in life. A further possibility is shown in the paper by McKenna *et al* (p 287) who describe two families with a clear history of sudden death.[20] At necropsy none of the victims, some of whom were adults, showed evidence of hypertrophy as assessed by left ventricular mass or shape but the percentage of myocyte disarray was well within the range characteristic of hypertrophic cardiomyopathy. These papers show that it is possible to have cases which have good cause to be considered as hypertrophic cardiomyopathy but do not actually have hypertrophy when this is defined as an increase in left ventricular mass or thickness.

The question remains whether there is one genetic abnormality encompassing all these different morphological and clinical expressions or whether there are several genetic abnormalities with a final common pathway of abnormal myocardial hypertrophy.

Identification of the gene or genes responsible would resolve the issue. A start has been made to identify by linkage studies the chromosomes responsible in affected families.[21] A site on chromosome 14 was identified in three families with considerable certainty. The genes for the heavy chains of cardiac myosin are on this chromosome. Further linkage studies will establish whether all affected families are the same and the relation of hypertrophic cardiomyopathy to conditions such as neurofibromatosis, Friedreich's ataxia, and Noonan's syndrome—all of which can cause a cardiac disease morphologically similar to hypertrophic cardiomyopathy. Initial results have identified one family with typical hypertrophic cardiomyopathy in which there is no linkage to a locus on chromosome 14 (W J McKenna, 1990, personal communication). This implies that at least two separate gene abnormalities can produce the disease known as hypertrophic cardiomyopathy.

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Br Heart J 1990;63:265–6

Editorial

Hypertrophic cardiomyopathy in the elderly

Hypertrophic cardiomyopathy, defined as idiopathic hypertrophy of a non-dilated ventricle, has a range of morphological and clinical features and can occur from infancy to old age.[1] Hypertrophic cardiomyopathy, although initially regarded as a rare disorder of young patients with symptoms, is probably not uncommon. In the early years, after the first descriptions of the disease, most clinical studies came from a few tertiary referral centres[2]—this biased selection towards young patients with symptoms who had a disease characterised by asymmetrical septal hypertrophy and dynamic left ventricular outflow tract obstruction.[3-5] Since then, however, it has become apparent, particularly with the widespread application of echocardiography, that hypertrophic cardiomyopathy occurs in patients of all ages with or without regional septal hypertrophy, an outflow tract gradient, or symptoms.[6-12]

Diagnosis

Echocardiography is now the technique of choice for the diagnosis and assessment of hypertrophic cardiomyopathy. The echocardiogram usually shows hypertrophy of the ventricular septum, but any region of the left ventricle (and occasionally the right ventricle) can be affected. Left ventricular contraction is hyperdynamic and there is often impaired and incoordinate relaxation and a reduced rate of filling.[13-16] These features are similar in all age groups, but in the elderly fibrous thickening of the ventricular septum in the area of mitral septal contact may be prominent and there can be quite extensive mitral annular calcification.[17] The aortic valve may also be calcified and regurgitant.

In a young patient, the echocardiographic finding of idiopathic left ventricular hypertrophy may lead with certainty to the diagnosis of hypertrophic cardiomyopathy; but in the elderly there are more frequent secondary causes of left ventricular hypertrophy. In particular, increasing age is clearly associated with increased left ventricular mass and septal thickness and changes in diastolic function.[18-22] In extreme old age, the septum may not only be hypertrophied but also sigmoid, which can also simulate the appearance of hypertrophic cardiomyopathy.[23] In children with clinical evidence or a family history of hypertrophic cardiomyopathy rapid development of left ventricular hypertrophy can be seen by echocardiography over four years. Increases in wall thickness of up to 23 mm have been noted.[24] In contrast, a similar study in 65 adults showed that none demonstrated an increase in left ventricular wall thickness and 14% had a significant reduction with relative enlargement of the left ventricular cavity.[25] In addition, echocardiographic measurements of left ventricular mass and maximum wall thickness were significantly higher in patients aged 21–30 than in older patients. Younger patients also had the most severe and diffuse hypertrophy in a study of 700 individuals with hypertrophic cardiomyopathy.[26] However, some patients, particularly women, may present in their sixth or seventh decade after a prolonged asymptomatic (latent?) period with progressive symptoms and often a poor response to medical treatment. Such patients may have a distinctive type of the disease, with modest septal hypertrophy, distortion of the left ventricular outflow tract, and a gradient generated by the posterior motion of the septum against the restricted movement of a calcified mitral valve.[17]

Prognosis

While premature sudden death is a well-known feature of hypertrophic cardiomyopathy it is relatively uncommon in patients with hypertrophic cardiomyopathy.[27,28] Sudden death is not confined to the young but most studies of the natural course of the disease have emphasised its rarity in elderly patients.[29,30] A retrospective analysis of 284 patients showed that sudden death was more common in those aged < 14 years and in older patients with symptoms. The annual mortality for cases diagnosed in childhood was 5·9% compared with 2·5% for cases in adults.[31] The better prognosis of elderly patients may reflect the survival of a subset of patients at low risk of sudden death, especially those with ventricular tachycardia or an adverse family history.[32,33] Lack of exertion in the elderly may also have a protective effect.

Hypertensive hypertrophic cardiomyopathy?

In 1957, when Brock first described an elderly patient with severe left ventricular hypertrophy and an outflow tract gradient, he concluded that the disease was secondary to hypertension[34]; this was not borne out in subsequent reports.[35,36] Though the morphological and echocardiographic features of hypertrophic cardiomyopathy and severe secondary left ventricular hypertrophy are usually distinctive,[37] diagnosis is complicated in mildly hypertensive patients with unequivocal echocardiographic features of hypertrophic cardiomyopathy in whom the degree of hypertrophy is inappropriate for the severity of hypertension. This problem was emphasised by the identification of 21, mostly elderly, female patients with severe concentric hypertrophy and small left ventricular cavity with hyperdynamic left ventricular contraction and abnormal diastolic function.[38] These patients usually presented in heart failure and their symptoms tended to be relieved by β blockade or calcium channel blocking drugs, rather than the traditional treatment of heart failure. This condition (hypertensive hypertrophic cardiomyopathy) suggests the coexistence of hypertrophic cardiomyopathy and hypertension. Among patients with hypertrophic cardiomyopathy those with hypertension tend to be older than those without. The clinical and echocardiographic features of hypertrophic cardiomyopathy were indistinguishable in those with hypertension and those without, except that hypertensive patients had thicker ventricular walls.[39,40] The wide variability of expression of hypertrophic cardiomyopathy implies that other stimuli to the expression of hypertrophy such as pressure overload and neurohormonal factors may be important in genetically susceptible individuals. Further careful clinical and genetic studies are required to clarify whether the definition of hypertrophic cardiomyopathy needs to be enlarged to include hypertension or whether hypertensive hypertrophic cardiomyopathy is a distinct clinical entity.

Treatment

Patients of all ages without symptoms or arrhythmias do not require treatment. Dyspnoea or angina are often adequately managed with β blockade or calcium antagonists[41 42] and amiodarone improves prognosis in patients with arrhythmias.[43] Surgery should not be excluded in the elderly because the results of myotomy and myectomy in those with outflow tract gradients (with or without concomitant coronary bypass grafting) are good.[44 45]

The presentation of an apparently congenital disorder in the elderly (without previous heart disease) is puzzling. While the elderly may present with typical symptoms of dizziness, syncope, breathlessness, chest pain, and palpitation the diagnosis is often delayed because these symptoms can be caused by coexisting disease. In addition, elderly patients can present in intractable heart failure caused by abnormalities of left ventricular relaxation and filling, and the diagnosis may be obscured by mitral regurgitation and mitral annular calcification. Although the distinctions between primary and secondary causes of hypertrophy are clear in young adults they are vague in the very young and the elderly. However, identification of the cause of hypertrophy probably has little influence on management.

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ORIGINAL ARTICLES

Six year follow up of a consecutive series of patients presenting to the coronary care unit with acute chest pain: prognostic importance of the electrocardiogram

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Abstract

In a retrospective 6 year follow up data were obtained for 536 of 566 (95%) consecutive patients admitted to a coronary care unit with acute chest pain. Their diagnoses were acute myocardial infarction in 290 (54%), myocardial ischaemia in 164 (31%), pericarditis in 16 (3%), and non-cardiac in 66 (12%). Six year mortality was 36%, 24%, 0%, and 16% respectively. In patients with acute myocardial infarction a higher mortality rate during follow up was associated with a higher than average age, a higher than average creatine kinase, previous myocardial infarction, Q wave infarction, and the presence of reciprocal changes. The presence of reciprocal changes was associated with higher than average concentration of serum creatine kinase, indicating more extensive infarction. Infarction complicated by ventricular fibrillation or left bundle branch block was associated with a higher death rate.

The electrocardiogram recorded at the time of acute myocardial infarction contains much useful prognostic information.

Several studies have reported mortality and prognostic patterns after myocardial infarction.[1-3] Fewer studies have examined mortality in patients with either a diagnosis of cardiac ischaemia without infarction[4-6] or "non-cardiac" chest pain.[7] Furthermore, although many studies have identified subgroups of patients at risk,[8] they have usually relied upon either predischarge or outpatient investigations.[9 10] Unfortunately, many deaths may occur before these investigations can be performed (and acted upon) so there is a need for a method of identifying high risk patients from the time of admission. The electrocardiogram recorded during the hospital stay is often neglected or passed over for more complex investigations, but we have found it to be a useful prognostic indicator despite previous reservations about its importance.[10-12]

To investigate these points we studied a consecutive series of patients presenting to a coronary care unit with acute chest pain who were followed up over a six year period.

Patients and methods

Over a one year period 566 consecutive patients presented to a coronary care unit with acute onset of chest pain. Follow up data were obtained for 536 (95%), who are the subjects of this report. Their mean age was 55 years (range 24–78 years); 399 were male and 137 were female. Details of the electrocardiogram on presentation and of any subsequent changes or arrhythmias during the hospital stay were recorded, together with personal details and past medical history. The patients were followed up retrospectively by reference to their hospital case notes or by contact with their general practitioners. Details of subsequent cardiovascular events and the cause of death were obtained wherever possible.

The diagnosis of acute myocardial infarction was made if two of the following were present: a characteristic history of more than 30 minutes chest pain, a rise in the concentration of serum creatine kinase of >75 U/l, and the development of characteristic echocardiographic changes. All the electrocardiograms were recorded in 12 lead format at a paper speed of 25 mm/s and 10 mm/mV.

We used the following definitions:

Q wave myocardial infarction. The development of abnormal Q waves in at least two adjacent infarct related leads.

Non-Q wave myocardial infarct. Important ST segment change or T wave inversion in at least two adjacent inferior leads or three adjacent anterior leads not progressing to the formation of abnormal Q waves, with these changes persisting for at least 24 hours.

"Enzymatic infarction". Acute chest pain with an abnormal rise of creatine kinase to at least twice the upper limit of normal but no significant electrocardiographic changes.

Reciprocal changes. ST segment depression >1 mm at or after 0·08 s from the J point of the QRS complex in leads VI–V3 in inferior infarcts and leads 2, 3, and aVF in anterior infarcts. Posterior infarcts all showed reciprocal changes (qv). Only those patients showing reciprocal changes within 24 hours of admission were included in this category.

Ischaemic heart disease presenting as ST segment depression of ≥ 1 mm and/or T wave flattening or inversion with no permanent ST or T wave changes and no abnormal rise in

Follow up data (mean 76 months (range 34–90)) on 536 patients with acute chest pain with various causes

Diagnosis	Number	Mean age	Mortality (%)	
			1 Month	6 Years
Myocardial infarction	290	54	14 (10–18)	36 (29–42)
Myocardial ischaemia	164	53	1 (0–3)	24 (17–31)
Non-cardiac	66	52	0	16 (6–25)
Pericarditis	16	47	0	0

95% Confidence intervals are shown in parentheses

serum creatine kinase despite a characteristic history of chest pain.

Pericarditis. Characteristic history and clinical signs plus concave ST segment elevation but no permanent electrocardiographic change or rise in creatine kinase.

"Non-cardiac" chest pain. A history of chest pain with no supporting electrocardiographic changes (including a predischarge exercise test) or abnormal rise of serum creatine kinase on that admission.

The arrhythmias recorded, whether transient or permanent, were atrial fibrillation, supraventricular tachycardia, complete atrioventricular block, left bundle branch block, frequent ventricular extrasystoles, ventricular tachycardia, or ventricular fibrillation.

The peak concentration of serum creatine kinase was recorded, the upper limit of normal being 75 U/l. An arbitrary distinction was made between mean peak enzyme concentrations above and below 1200 U/l, indicating larger or smaller infarcts respectively.

All patients with a diagnosis of myocardial infarction underwent a limited exercise test before discharge. Any patients who did not complete this satisfactorily were started on a β blocker and examined by cardiac catheterisation. They progressed to either bypass surgery or continued on medical treatment as appropriate. Patients with a diagnosis of ischaemic heart disease also underwent a full exercise test before discharge. If appropriate they had cardiac catheterisation.

Results were analysed by standard life tables calculated on a monthly basis. We compared groups by means of the log rank test.[13]

Results

Follow up data for a mean of 76 months (range 34–90 months) were obtained for 536 out of 566 (95%) patients with the diagnoses of acute myocardial infarction, ischaemic heart disease, pericarditis, and "non-cardiac" chest pain. The table shows the 6 year mortality and figure 1 the life tables. In 11 out of 66 patients with a "non-cardiac" diagnosis for the index event manifestations of ischaemic heart disease developed during follow up.

Survival after myocardial infarction was significantly worse than after the diagnoses of ischaemic heart disease ($\chi^2 = 8·7$; $p < 0·01$) but survival after a "non-cardiac" diagnosis was not significantly different from that after a diagnosis of ischaemic heart disease ($\chi^2 = 1·9$; NS).

MYOCARDIAL INFARCTION

There were 194 patients with Q wave myocardial infarction (31 had had a previous myocardial infarct), 52 with non-Q wave infarcts, and 44 "non-specific" infarcts. Five of the 44 were "enzymatic infarcts", nine had left bundle branch block, and in 30 electrocardiographic data were incomplete. Thus complete electrocardiograpic data were available for 260 of the 290 patients with acute myocardial infarction.

In the first month mortality from myocardial infarction was 14% with a uniform annual mortality of 3·3% thereafter. There was no difference in mortality between the sexes and mortality during the first year was no different from that in subsequent years.

EFFECT OF AGE (fig 2)

Mortality was significantly higher for those patients aged above the median of 56 years at the time of myocardial infarction than in those aged 56 or below (44% *v* 27% respectively)($\chi^2 = 14·1$; $p < 0·001$).

PREVIOUS INFARCTION

Mortality was higher for those with previous infarction than in those without previous infarction ($\chi^2 = 4·5$; $p < 0·05$).

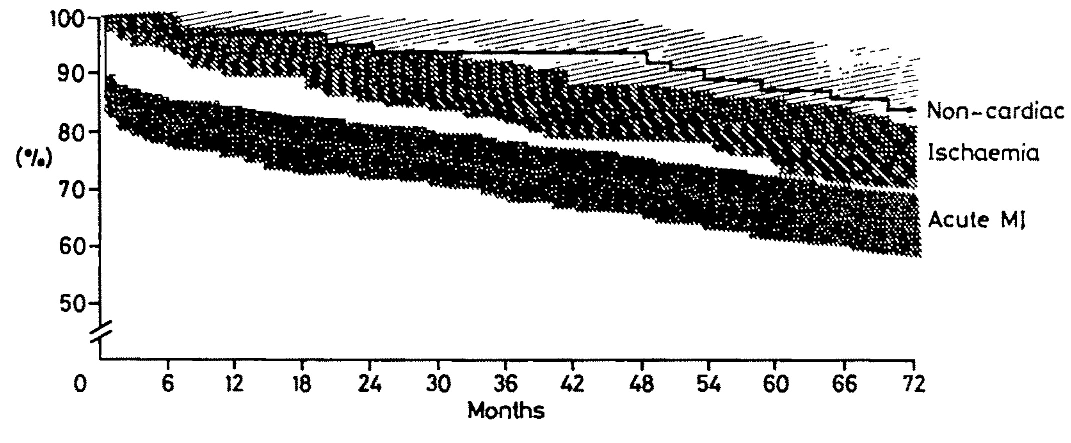
SEX

There was no significant difference in mortality from myocardial infarction for men and women ($\chi^2 = 0·0$; NS).

CREATINE KINASE ABOVE AND BELOW 1200 U/L

For the patients with full data on enzyme concentrations, the median serum creatine kinase concentration was 1200 U/l. One hundred and twenty nine patients had a serum creatine kinase concentration of less than this median value; their 6 year mortality was less than that

Figure 1 Survival curves for acute myocardial infarction (MI), ischaemic heart disease, and "non-cardiac" pain (95% confidence intervals are shown as shaded areas)



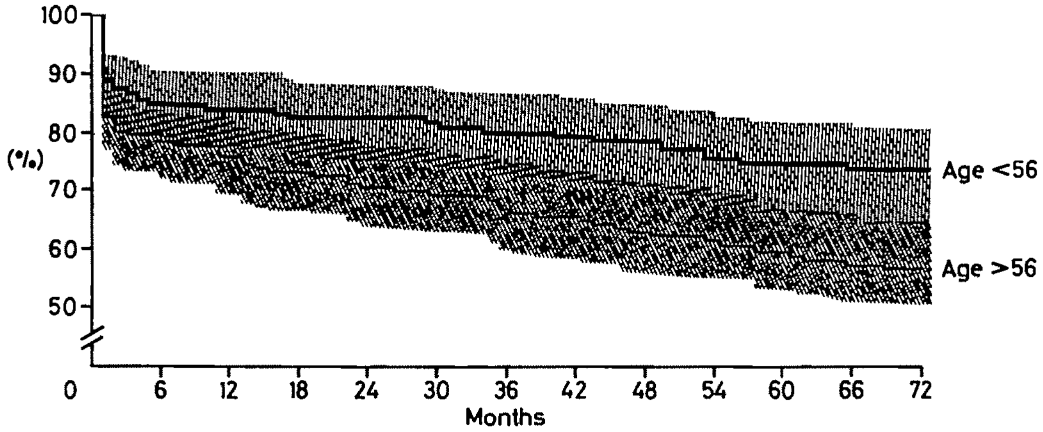


Figure 2 Survival curves for patients with myocardial infarction aged <56 years and >56 years (95% confidence intervals are shown as shaded areas).

of the 135 patients with a value of $\geqslant 1200$ U/l (23% v 42% respectively) ($\chi^2 = 10{\cdot}9$; $p < 0.001$) (fig 3). The mean age in both groups was 55.

SITE OF INFARCTION

The site of infarction was anterior in 147 (50%), inferior in 103 (36%), posterior in 16 (6%), and uncertain in 24 cases (8%). There was no significant difference in mortality between patients with anterior or inferior infarctions ($\chi^2 = 0{\cdot}5$; NS).

RECIPROCAL CHANGES

Two of the 260 patients with electrocardiographic evidence of myocardial infarction were excluded because the first electrocardiogram available for analysis was performed more than 24 hours after admission. The 105 patients with reciprocal changes had a higher mortality than the 153 patients without reciprocal changes ($\chi^2 = 10{\cdot}9$; $p < 0{\cdot}001$) (fig 4). The mean age was 55 in each group but the mean concentration of serum creatine kinase was higher in those patients with reciprocal changes than those without (1999 v 1279 U/l; $p < 0{\cdot}001$). Only eight of 105 patients with reciprocal changes had previously had a myocardial infarction compared with 25 of 153 patients without reciprocal changes ($\chi^2 = 4{\cdot}2$; $p < 0.05$).

Q AND NON-Q WAVE INFARCTS

Mortality was significantly lower in the 52 patients with non Q wave infarcts than in those with Q wave infarcts ($\chi^2 = 9{\cdot}8$; $p < 0{\cdot}01$) (fig 5). The patients with non-Q wave infarcts also had lower mean concentrations of creatine kinase than those patients with Q wave infarcts (1016 v 1689 U/l, $p < 0{\cdot}001$).

MYOCARDIAL INFARCTION COMPLICATED BY ARRHYTHMIAS

Ventricular fibrillation occurred in 35 patients, in whom the mean serum concentration of creatine kinase was 3246 U/l. Mortality was higher than in patients with myocardial infarction without this complication ($\chi^2 = 20{\cdot}2$; $p < 0.001$) (fig 6).

Myocardial infarction was complicated by ventricular tachycardia in 16 patients and by transient or permanent atrial fibrillation in 17 patients. In neither case was survival significantly different from that in patients without these complications ($\chi^2 = 3{\cdot}3$ and $0{\cdot}5$ respectively).

Ten patients had left bundle branch block (seven died during the first month of follow up)—a significantly worse survival rate than in those without this complication ($\chi^2 = 9{\cdot}6$, $p < 0{\cdot}01$).

Discussion

EFFECT OF INFARCT SIZE AND PREVIOUS MYOCARDIAL INFARCTION ON OUTCOME

The prognosis after myocardial infarction is strongly related to residual ventricular function.[9] Patients with larger infarcts or prior myocardial infarction would, therefore, be expected to have a worse prognosis[14-16] because

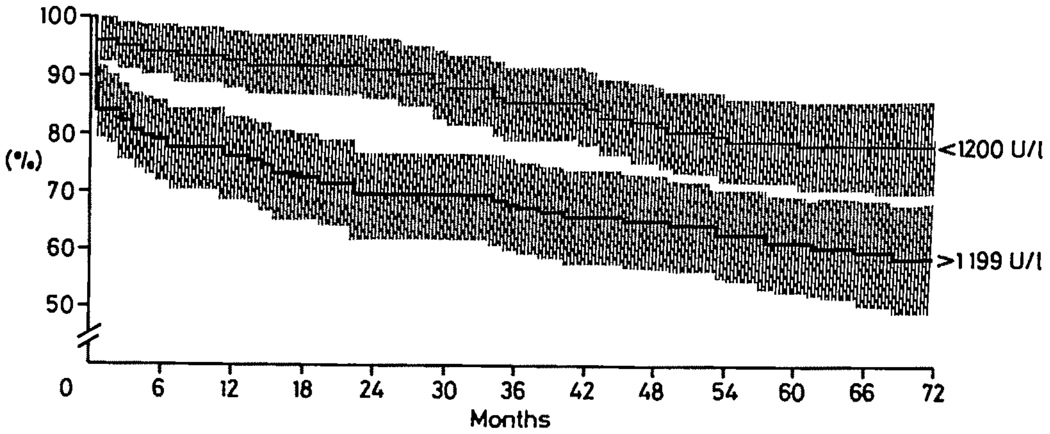


Figure 3 Survival curves for patients with serum concentrations of creatine kinase <1200 U/l and >1199 U/l (95% confidence intervals are shown as shaded areas).

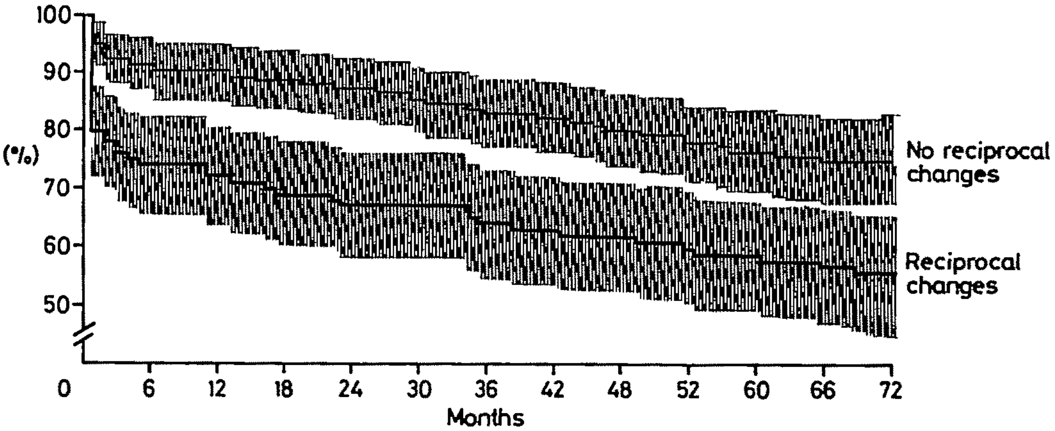


Figure 4 Survival curves for patients with and without reciprocal changes (95% confidence intervals are shown as shaded areas).

more extensive damage is associated with pump failure and ventricular fibrillation.[9 17 18] This is clearly shown in our study where the prognosis was worse for patients with prior myocardial infarction or with serum concentrations of creatine kinase above the median value.

RECIPROCAL CHANGES

The cause of the reciprocal changes seen on the electrocardiogram in acute myocardial infarction is still a matter of debate[19 20] but there is evidence of associated increased mortality.[8] One view is that reciprocal change is purely an electrophysiological phenomenon,[20] while an alternative view is that it indicates more extensive ischaemia or infarction.[18 19]

If recriprocal change results from more extensive ischaemia or infarction, then patients showing this would be expected to have higher serum concentrations of cardiac enzymes and a worse prognosis; this is what we have shown. Interestingly, those patients showing reciprocal changes had significantly fewer previous infarctions, so for that reason this group would have been expected to have had a better prognosis. There was no significant age difference between the two populations to account for our findings. These data, therefore, strongly support the view that the presence of reciprocal changes acts as an early and independent marker for those patients at particularly high risk. This excess risk is manifested within the first month and continues thereafter.

SEX AND SITE OF INFARCTION

It has been suggested that women have a worse prognosis than men after myocardial infarction.[21 22] Our data do not support this. The apparent difference in mortality between the sexes reported by others was most probably the result of the higher mean age of the women.[23]

In the past it was considered that anterior myocardial infarction carried a worse prognosis than inferior infarction,[3 14 21] although more recently this has been refuted.[24] We found no significant difference in mortality between the sites of infarction.

Q WAVE AND NON-Q WAVE INFARCTION

There is still debate over the prognosis of patients with subendocardial infarction. It is widely believed that although there is a smaller initial mortality than for transmural infarctions, there is a substantial subsequent risk because many of these patients progress to transmural infarction.[25-27] If this were so then the survival curves for these two groups would tend to converge.[27] Definitions of non-transmural infarction vary,[28] and to complicate matters still further many transmural infarctions diagnosed at necropsy have not produced Q waves on the surface electrocardiogram.

We did not see convergence of survival curves and a lower mortality was seen in the non-Q wave group, presumably reflecting the smaller infarcts.[28] In patients with non-transmural infarction, as we define it, there appears to be no reason for early investigation. This conclusion is supported by an extensive review of published reports[29] and one large recent study[28] which showed a better prognosis in patients with subendocardial infarction.

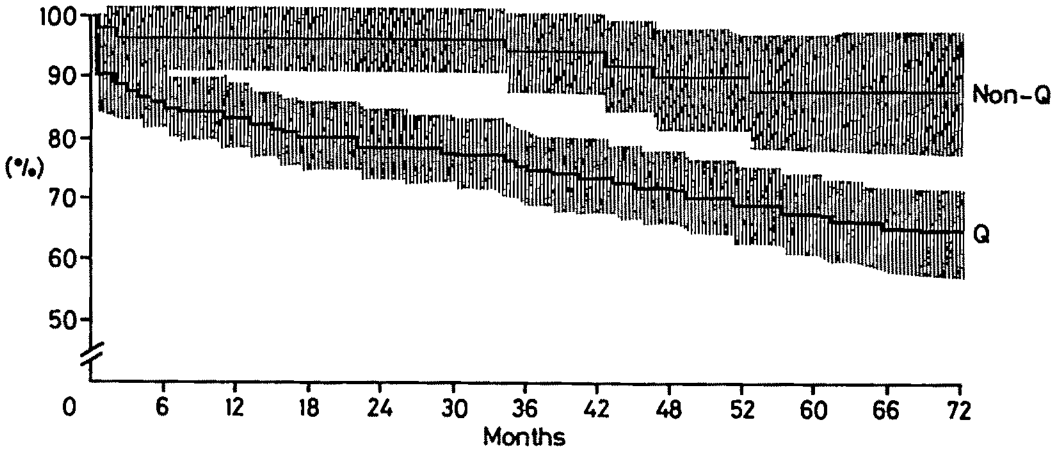


Figure 5 Survival curves for patients with Q wave and non-Q wave infarctions (95% confidence intervals are shown as shaded areas).

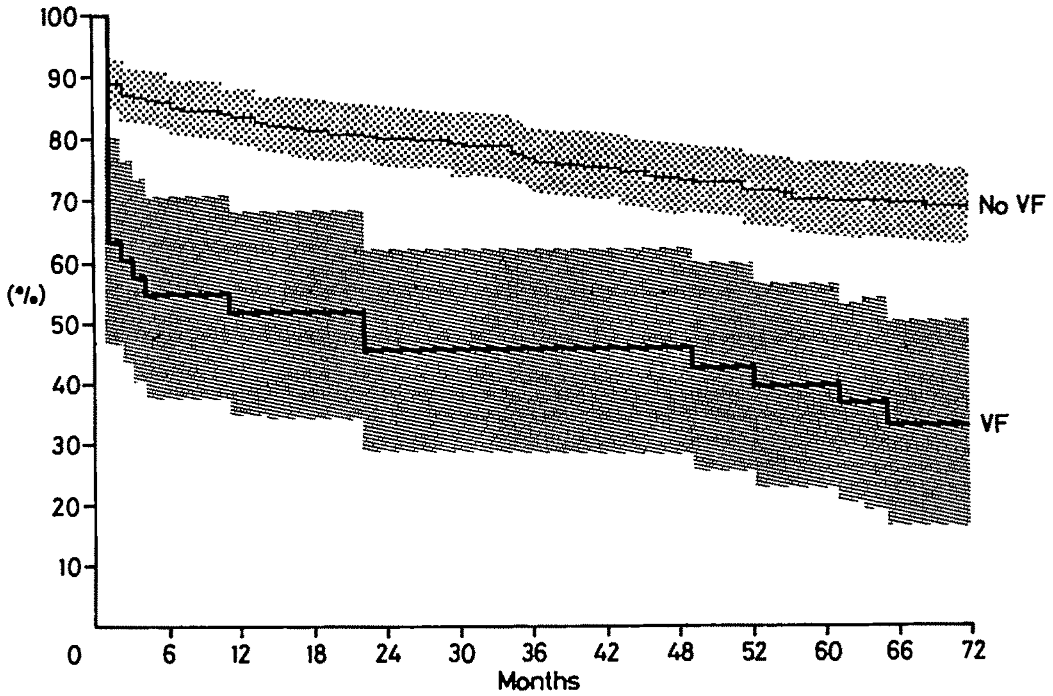


Figure 6 Survival curves for patients without ventricular fibrillation and with ventricular fibrillation (95% confidence intervals are shown as shaded areas).

MYOCARDIAL INFARCTION COMPLICATED BY VENTRICULAR FIBRILLATION

If very early ventricular fibrillation is successfully treated it is not generally thought to carry such an adverse prognosis as later ventricular fibrillation.[30] We did not distinguish between those patients with very early and those with later ventricular fibrillation but in view of the small numbers it is unlikely tht such analysis would have been conclusive. However, the larger an infarct the greater the likelihood of ventricular fibrillation developing.[31] In this study the patients in whom ventricular fibrillation developed had a mean serum concentration of creatine kinase that was twice that for all infarcts, and mortality was significantly worse than for patients without ventricular fibrillation.

CARDIAC ISCHAEMIA

The prognosis of patients with chronic angina is usually thought to be quite good, and many hundreds of patients have been repeatedly exercised to induce angina, either during pharmaceutical studies or to improve exercise tolerance, without coming to harm.[32 33]

In our patients with a diagnosis of ischaemic heart disease outcome was not good. Although their initial mortality was low, their subsequent 6 year mortality was only one third less than that for patients with infarcts. Some might suggest that it is only the subset of patients who get admitted with unstable or severe angina that is at risk, but this is not supported by community studies. For example, Hobkirk followed up 307 out of 336 patients known to have chronic angina. Four years later 12% had died and 6% had undergone bypass grafting.[5] Campbell *et al* followed up 1428 women with angina; by 12 years there was a 50% increase in their expected mortality.[34]

It has been postulated that patients with a history of chronic angina before infarction might have smaller infarcts and a better prognosis than patients without angina.[35] In theory, chronic angina should lead to the development of collateral vessels which protect the jeopardised myocardium.[36 37] Our own and previous studies, however, do not support this hypothesis.[1 3 21]

"NON-CARDIAC" CHEST PAIN

Patients with a diagnosis of "non-cardiac" pain or "chest pain ? cause" are generally thought to have a good prognosis. Our study clearly showed that for our patients this was not so; the 6 year mortality (16%) differed only marginally from that in patients diagnosed as having ischaemic heart disease. Smyllie reported similar results.[7] In Smyllie's study at 6 years there was a 12% mortality for patients discharged with a diagnosis of angina and a 10% mortality for patients diagnosed as having "non-cardiac" pain. Wilcox *et al* noted a low one year mortality in patients with "non-cardiac" chest pain,[38] which we have confirmed; but later manifestations of ischaemic heart disease suggest that in some cases the "non-cardiac" diagnosis was mistaken. Our results suggest that patients with "non-cardiac pain" should perhaps be followed up more closely.

The electrocardiogram recorded at the time of acute myocardial infarction is of considerable prognostic value and could be used to identify patients who might benefit from early investigation and intervention. If the electrocardiogram shows reciprocal changes, or where infarction is complicated by ventricular fibrillation or left bundle branch block, patients are at particular risk. On the other hand, patients without reciprocal changes and those with non-Q wave infarction are at relatively low risk. Patients in whom myocardial infarction is not confirmed, who are discharged with a diagnosis of ischaemic heart disease or "non-cardiac" pain, nevertheless, have an appreciable long term risk.

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Effect of thrombolysis on the evolution of late potentials within 10 days of infarction

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Abstract

Patients with late potentials in the signal averaged electrocardiogram are more at risk of lethal arrhythmias in the period after acute myocardial infarction. To test the effects of thrombolysis on the incidence and evolution of late potentials, 158 consecutive patients were prospectively studied during the first 10 days after acute myocardial infarction. The study population consisted of two groups: 93 control patients treated conservatively and 65 patients treated with intravenous thrombolysis. Recordings of signal averaged electrocardiogram were obtained within two days and 7–10 days after infarction. The incidence of late potentials in the first two days after infarction was not significantly different in the thrombolytic and control groups (14% *v* 11·8%). By 7–10 days the incidence of late potentials among patients who underwent thrombolysis remained unchanged (14%); however, it increased significantly in the control group (11·8% to 22·5%).

Thus thrombolysis seems to reduce the evolution of late potentials within 10 days of infarction. Because the risk of fatal arrhythmias is higher in patients with late potentials this study may partly explain the reduced mortality after thrombolysis.

Ventricular late potentials consist of low amplitude high frequency electrical signals that occur at the end of the QRS complex or during the ST segment. These signals probably arise from areas of slow conduction in diseased myocardial regions and may thus be markers of arrhythmogenic features.[1] Late potentials present within 1–4 weeks after acute myocardial infarction predicted a higher risk of sudden cardiac death and ventricular tachycardia in the next 6–24 months.[2] Recently, thrombolytic treatment within a few hours of acute myocardial infarction has been established as an effective means of improving survival[3 4] and preserving myocardial function[5 6] in the acute and chronic phases of infarction. However, there are few data on the incidence, course, and the effects of thrombolysis on late potentials in the early post-infarction period. We have evaluated the effects of thrombolytic treatment on the incidence and evolution of late potentials during the first 10 days after acute myocardial infarction.

Patients and methods

Our prospective study included 158 consecutive patients with first acute myocardial infarction who underwent two signal averaged electrocardiogram recordings, the first within two days and the second within 7–10 days of the acute myocardial infarction. We excluded patients with a QRS complex lasting $\geqslant 110$ ms or atrial fibrillation on an admission surface electrocardiogram. There were 138 men and 20 women (mean (SD) age 60 (8) years). Anterior acute myocardial infarction was diagnosed in 60 and inferior acute myocardial infarction in 98 patients. The diagnosis of acute myocardial infarction was based on prolonged (>30 minutes) chest pain, ST elevation of $\geqslant 1$mV in at least two leads on the admission electrocardiogram, and a raised serum concentration of creatine kinase of myocardial origin.

Intravenous thrombolytic agents were given to 65 patients within four hours of the acute myocardial infarction: 24 were treated with streptokinase (1·5 million units) and 41 with tissue plasminogen activator (120 mg) (thrombolysis group). In 49 patients reperfusion was successful and in 16 it was not. Successful reperfusion was defined as an abrupt decrease in chest pain and a decrease of ST segment elevation by at least 50% within 30 minutes of administration of the thrombolytic agent associated with early peaking of creatine kinase MB (within 9–12 hours). Ninety three patients did not receive thrombolytic agents (control group) either because they arrived too late at the hospital (chest pain for more than four hours) or because of conventional contraindications to thrombolytic treatment. The mean (SD) left ventricular ejection fraction determined 2–10 days after infarction by the multiple gated acquisition technique was significantly higher in successful reperfusion than unsuccessful reperfusion and control patients (57·4 (10·1)% *v* 42·3 (14·7)% and 42·3 (15)%, respectively, $p < 0·05$). No other clinical variables were significantly different among the groups (table 1).

Signal averaging was obtained by the Hypec analyser (Aerotel, Israel), which allows separate averaging of the 12 electrocardiographic leads. The system uses a non-recursive (finite impulse response) digital filter provided by fast Fourier transformation algorithm which allows for a zero phase delay and prevention of the ringing phenomenon without the use of bidirectional signal processing.[7] Normal values for signal averaged electrocardiogram were measured in 25 normal subjects, 22

Table 1 Clinical variables of the study groups

Variable	*Thrombolysis* *Successful*	*Thrombolysis* *Unsuccessful*	*Control*
Patients	49	16	93
Age (mean (SD))	58 6 (10)	61 (6·25)	61 (9)
Men	42	15	81
Women	7	1	12
Anterior MI	21	8	31
Inferior MI	28	8	62
LVEF % (mean (SD))	57 4 (10 1)	42 3 (14 7)	42·3 (15·0)

LVEF, left ventricular ejection fraction, MI, myocardial infarction

Table 2 Frequency of late potentials in thrombolysis and control groups

Treatment	*2 days* *n (%)*	*7–10 days* *n (%)*
Thrombolysis:		
Total	9/64 (14)	9/64 (14)
Successful	5/49 (10 4)	5/49 (10 4)
Unsuccessful	4/16 (25)	4/16 (25)
Control:		
Total	11/93 (11 8)	21/93 (22 5)

patients after infarction, and 14 patients with ventricular tachycardia or fibrillation after infarction. Accordingly, late potentials were defined as filtered (60–200 Hz) QRS complexes lasting $\geqslant 110$ ms with a root mean square voltage in the last 40 ms of the QRS complex (RMS$_{40}$) of $\leqslant 10$ µV in at least two adjacent electrocardiographic leads.

We used the McNemar test for significance of changes[8] for statistical analysis of the difference between the occurrence of late potentials on the first and subsequent signal averaged electrocardiograms. The Mann-Whitney U test was used to compare the distribution of QRS duration and RMS$_{40}$ in both groups.

Results

Table 2 shows the frequency of late potentials. Figures 1 and 2 show signal averaged electrocardiograms with and without late potentials.

The mean (SD) duration of the QRS complex was significantly shorter after successful reperfusion than in the control group in seven out of 12 leads recorded within two days (for example in lead II 96 (8) *v* 101 (13) ms, p < 0 05) and in 10 of 12 leads within 7–10 days (for example in lead II 99 (8) *v* 106 (19) ms, p < 0·05). There were no significant differences in RMS$_{40}$ between the groups. For example, in lead II RMS$_{40}$ was 19 (10) *v* 21 (14) µV within two days and 20 (10) *v* 19 (13) µV within 7–10 days in the successful reperfusion and control groups respectively. No significant differences in QRS duration and RMS$_{40}$ were found between patients in whom thrombolysis was unsuccessful and the controls.

In the first signal averaged electrocardiogram (recorded within two days of infarction) the frequency of late potentials was similar in the thrombolysis and control groups (14·0% and 11·8% respectively). In the second signal averaged electrocardiogram (recorded within 7–10 days) there was a significant increase in the frequency of late potentials among control patients (from 11·8% to 22·5%, p < 0·01), whereas the frequency of late potentials in the thrombolysis group remained at 14%. In patients showing successful reperfusion late potentials disappeared in two patients in the second signal averaged electrocardiogram while in two other patients late potentials were detected for the first time in the second (7–10 days) signal averaged electrocardiogram recording. In patients in whom reperfusion was unsuccessful and in control patients late potentials recorded within two days were still present in the signal averaged electrocardiogram performed 7–10 days after the acute myocardial infarction. The difference in the frequency of

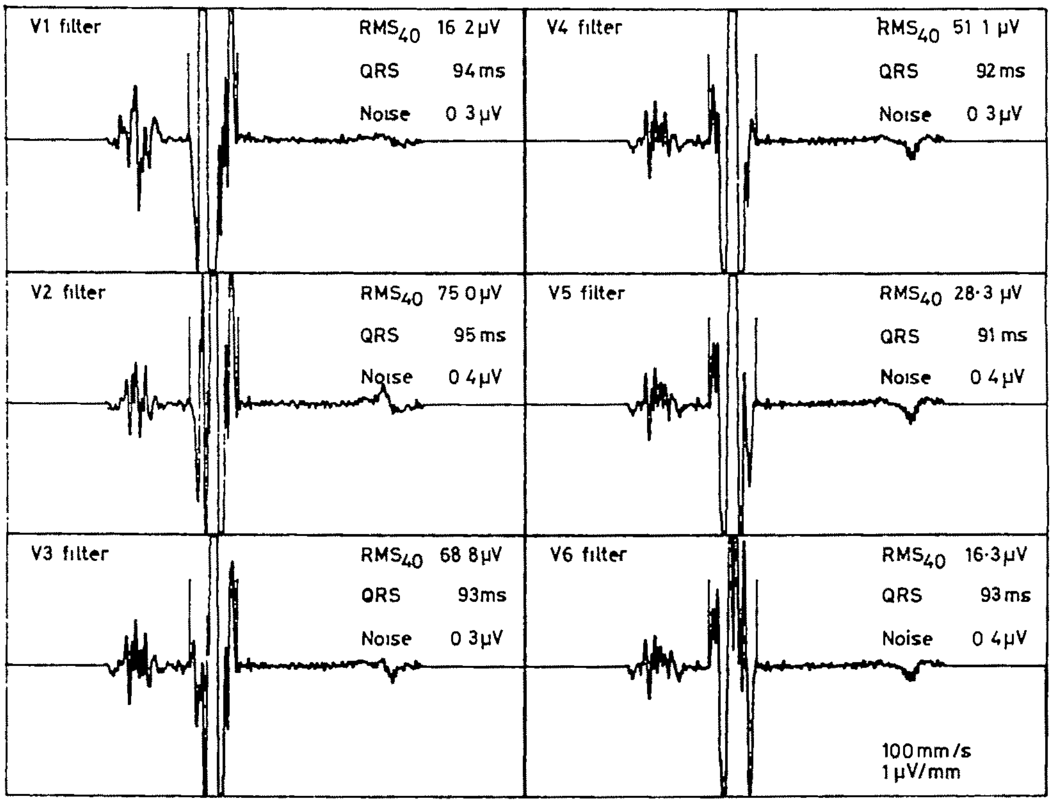

Figure 1 Signal averaged electrocardiogram of six precordial leads recorded from a patient with successful reperfusion. Late potentials were not present and QRS duration and RMS$_{40}$ were normal in all leads.

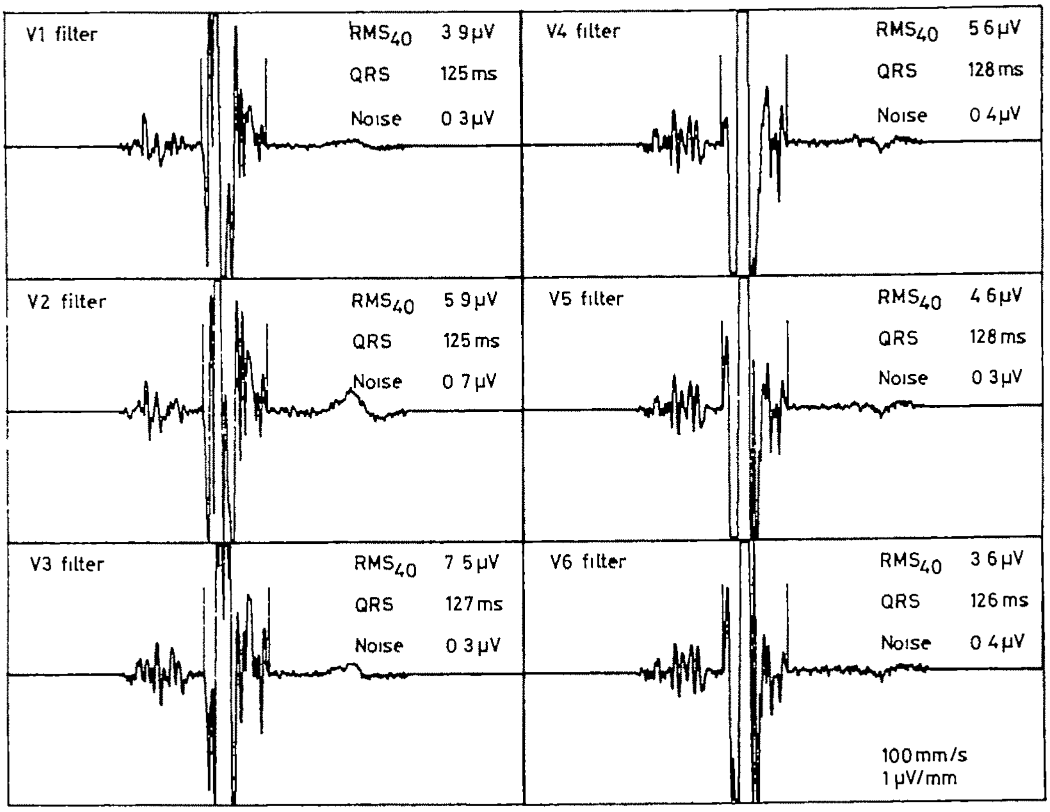

Figure 2 Signal averaged electrocardiogram of six precordial leads in a patient who was not treated with thrombolytic agents Late potentials are clearly detected at the end of the filtered QRS complexes. The abnormally long QRS duration and low RMS_{40} values are given for each lead

late potentials between patients in whom reperfusion was successful or unsuccessful (10·4% *v* 25·0%) was not statistically significant (p = 0 11).

Discussion

This study indicates that patients treated with thrombolytic agents within four hours of an acute myocardial infarction are "protected" from the increase in the frequency of late potentials that occurs in patients not treated by thrombolysis. Irwin *et al* and Volosin *et al* reported that late potentials that presented within a few hours of acute myocardial infarction regressed within seven days of successful reperfusion.[9 10] The difference with our observations may reflect differences in methods. Both groups[9 10] performed the first signal averaged electrocardiogram earlier than we did, at a time when dynamic changes in the border zone of the acute myocardial infarction are likely. In addition, Irwin *et al* used RMS_{40} $\leqslant 25$ µV as the sole criterion for late potentials,[9] while criteria for late potentials were not reported by Volosin *et al.*[10] Like us, Gang *et al* found a reduced incidence of late potentials among successfully reperfused patients.[11]

To detect late potentials we averaged 12 electrocardiogram leads filtered at a cut off of 60 Hz by a non-recursive digital filter. This method differs from Simson's technique, which is based on the orthogonal (XYZ) lead system, with a bidirectional filter at a cut off of 40 Hz. Our own (unpublished) data and those of others[12 13] show a comparable or higher detection of late potentials with a multilead rather than a composite XYZ vector. A 60 Hz cut off is within the accepted range of filters used for the detection of late potentials.[14] We sought an abnormal RMS_{40} and QRS duration in two adjacent leads because we had never found these two features in two or more adjacent leads in healthy individuals.

Our study indicates that thrombolytic treatment may enhance electrical stability, as reflected by the decreased frequency of late potentials. The present study does not establish whether this is an independent effect on the ventricular electrical characteristics or a result of enhanced myocardial salvage (shown by the higher left ventricular ejection fraction after successful reperfusion). This would require a long term study. Several studies showed fewer spontaneous severe arrhythmias and less inducibility of ventricular tachycardia by programmed ventricular stimulation in patients who had undergone thrombolytic treatment.[15-17] Our data accord with these observations of increased electrical stability, which may be partly responsible for the enhanced survival of patients who undergo thrombolytic treatment for acute myocardial infarction.

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Sustained improvement in left ventricular function after successful coronary angioplasty

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Abstract

The short and long term effects of successful percutaneous transluminal coronary angioplasty on left ventricular function at rest and on exercise were investigated in 49 patients. Thirty four had had no previous infarction (group 1) and 15 had (group 2). Technetium-99m gated blood pool images were obtained at rest and during exercise before, six weeks after, and a mean of fifteen months after successful angioplasty. Before angioplasty the mean (SD) ejection fraction fell significantly on exercise in both groups from 58 (10)% to 53 (13)% in group 1 and from 48 (10)% to 40 (16)% in group 2. This change was paralleled by a worsening wall motion score (from 0·6 (0·4) to 1·6 (1·2) in group 1 and from 2·3 (1·9) to 3·3 (2·4) in group 2). Six weeks after the procedure there was little change in resting ejection fraction but it increased significantly on exercise (to 62 (11)% in group 1 and to 53 (13)% in group 2). There was a concomitant significant improvement in the exercise wall motion score (to 0·4 (0·6) in group 1 and to 1·8 (1·1) in group 2). This improvement in exercise ejection fraction and wall motion was maintained at later follow up with no significant deterioration in either variable and a clearly sustained improvement in ejection fraction (60 (10)% in group 1 and 51 (10)% in group 2) and wall motion score (0·2 (0·2) in group 1 and 1·3 (0·8) in group 2) compared with values before angioplasty.

The initial improvement in left ventricular function on exercise after successful angioplasty was maintained for at least 9–24 months both in patients with previous myocardial infarction and in those without.

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Coronary angioplasty is now a well established treatment for atheromatous coronary artery disease and has been shown to be efficacious in a wide variety of clinical circumstances.[1-3] A technically successful procedure was usually associated with an immediate improvement in patients' symptoms, exercise tolerance, and myocardial perfusion.[4 5] There was also evidence of a short term improvement in left ventricular function on exercise though there was little change in resting function.[6-8]

Long term clinical and angiographic follow up of percutaneous transluminal coronary angioplasty is now well documented. There was a 30% incidence of early restenosis, but a successful procedure was associated with lasting relief of angina for up to eight years with a small percentage of patients developing new disease in other segments of the coronary circulation.[9] There are few studies of long term changes in left ventricular function after successful angioplasty. Kent and coworkers followed up 19 patients for six months after successful primary angioplasty and showed sustained improvement in left ventricular function on exercise over this period.[6] The long term benefits of angioplasty in patients who have poor resting left ventricular function have not been specifically examined.

We obtained gated blood pool images from 58 patients at rest and during exercise before and six weeks after a successful angioplasty procedure. Those who remained symptom free (49) were reinvestigated by the same technique 9–24 months (mean 15 months) after the procedure to assess the long term changes in left ventricular ejection fraction and wall motion. The patients were analysed as two groups, according to whether or not they had sustained a previous myocardial infarction. We did this to study the benefits in patients with poor initial resting left ventricular function.

Patients and methods

PATIENTS

A total of 58 patients underwent gated blood pool studies at rest and on exercise before and six weeks after a successful coronary angioplasty procedure. In seven of these patients restenosis of the target vessel developed during the follow up: five had repeat angioplasty and two underwent coronary artery bypass grafting. New disease developed in one patient who then underwent grafting and one patient moved from the region and was lost to follow up. Thus of the original 58 patients there were 49 with no evidence of any cardiac event or clinical/angiographic evidence of restenosis who were followed up. All of them initially presented with chronic stable angina refractory to medical treatment. The mean age of the group was 54 years and the ratio of males to females was 5:1. Thirty four patients had no previous history of myocardial infarction and fifteen had had previous Q wave infarction. Because the presence of previous infarction is likely to influence resting and

Age, sex, and target vessel in both groups of patients

	No previous MI (group 1)	*Previous MI (group 2)*
Number	34	15
M F	6 1	4.1
Age (mean) (yr)	52	56
Target vessel:		
LAD	19 (56%)	11 (73%)
RCA	12 (35%)	2 (14%)
Cx	3 (9%)	2 (13%)
Multivessel PTCA	5	0

Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery, PTCA, percutaneous transluminal coronary angioplasty

exercise left ventricular function groups 1 and 2 will be considered separately.

The table shows the patients' characteristics and target vessels. The two groups of patients share similar baseline characteristics. More patients in group 2 had disease of the left anterior descending coronary artery but this difference was not statistically significant. All the patients in group 2 underwent angioplasty to the infarct related vessel. Five patients in group 2 had a second vessel dilated. The mean percentage stenosis of the normal vessel diameter was 87% in group 1 and 82% in group 2. This was reduced to a mean value of 15% in both groups after successful dilatation.

Follow up gated blood pool studies were carried out a mean of 15 months after the angioplasty procedure (range 9–24 months) as described below.

GATED BLOOD POOL STUDIES

Three sets of radionuclide images were obtained at rest and on exercise in each patient. Antianginal medication, apart from sublingual nitrate, was stopped 48 hours before each investigation and patients attended in a preabsorbtive state. Red cells were labelled in vivo with 740 mBq of technetium-99m pertechnetate 20 minutes after the administration of stannous chloride. Images were acquired with a Picker mobile gamma camera with a high sensitivity collimator electrocardiographically gated at 24 frames per cardiac cycle. Images at rest were obtained over 2 minutes with patients supine and the camera in the 30° left anterior oblique position with 5°–10° of caudal tilt to obtain maximal chamber separation with clear septal separation of the right and left ventricles. The camera angles were noted and were repeated for any individual patient in subsequent studies.

Graded exercise images were obtained with the patient in the same position on a bicycle ergometer, starting at 25 W and increasing by 25 W until the onset of angina or to a maximum of 100 W. Each exercise level was maintained for three minutes to allow one minute to reach equilibrium and a 2 minute image acquisition period. At six week and long term follow up all but five of the patients were able to exercise to a higher level than at the initial investigation (40 to one 25 W increment and four to two 25 W increments).

Data were analysed on a DEC 11 computer, and the global ejection fraction was calculated at rest and maximum exercise by a semi-automated edge detection algorithm that compensated for a moving region of interest. A wall motion image was generated and displayed on a closed loop cine. The left ventricle was divided into three regions of interest: free wall, apex, and septum. Each segment was graded from 0 to 4 where 0 = normal wall motion and 4 = frank dyskinesia. Images were examined by two experienced observers. Linear regression analysis of the interobserver scores gave correlation coefficients of 0·94 and 0·85 for ejection fraction and wall motion analysis respectively.

CORONARY ANGIOPLASTY

Angioplasty was carried out by one of two principal operators via the transfemoral route in all patients. A steerable balloon system was used and patients were treated with aspirin (300 mg once a day), nifedipine (10 mg three times a day), isosorbide dinitrate (10 mg three times a day), intravenous nitrates, and heparin during the procedure. A successful procedure was defined as a reduction of the percentage stenosis to <50% of the diameter of the nearest normal vessel segment with no major complication such as myocardial infarction, emergency or elective coronary artery bypass grafting, or death.

STATISTICAL ANALYSIS

Values for the groups are expressed as mean (SD). Data at rest and on exercise before and after angioplasty were compared by Student's paired t test. Differences in baseline patient characteristics were evaluated by χ^2 testing. All statistical analysis was performed with the Minitab statistics package (Minitab, State College, Pennsylvania 16801).

Results

Figures 1 and 2 show the short and long term changes in left ventricular function.

GROUP 1

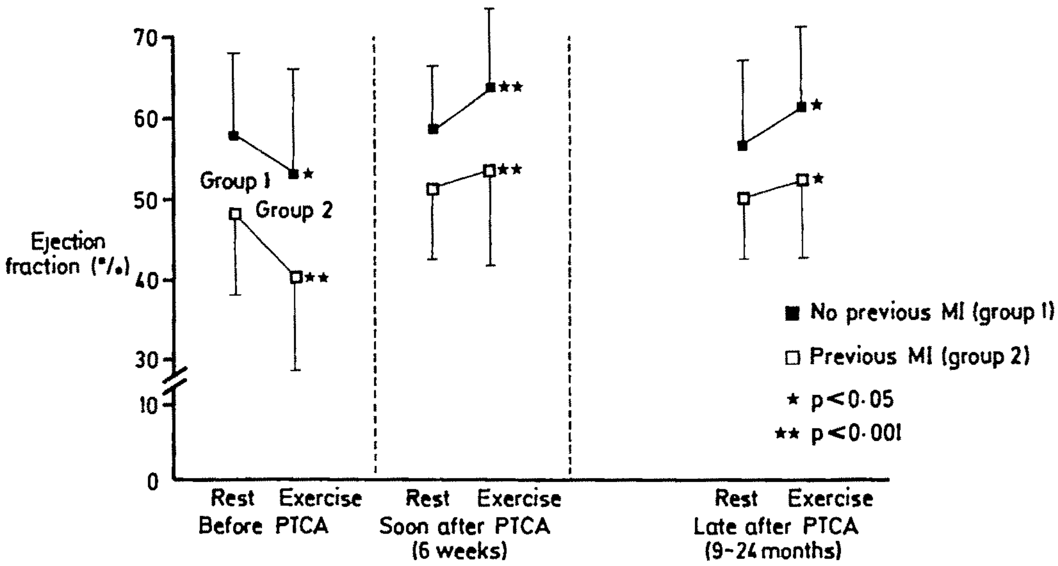
Before angioplasty the mean resting ejection fraction in patients without previous myocardial infarction was 58 (10)% and this fell on exercise to a mean of 53 (13) ($p < 0·05$). Six weeks after successful angioplasty the resting ejection fraction was unchanged (58 (8)%) but there was a significant rise in the exercise ejection fraction to 62 (11)%. These changes were paralleled by the changes in mean wall motion score—0·6 (0·4) and 1·6 (1·2) at rest and on exercise before angioplasty and 0·3 (0·4) and 0·4 (0·6) after angioplasty.

At long term follow up the mean resting ejection fraction was 53 (8)% and the improvement in mean exercise ejection fraction over values before angioplasty was maintained (60 (10)% ($p < 0·002$). At long term follow up the mean resting wall motion score was 0 2 (0·3) and on exercise it was 0·2 (0·2).

GROUP 2

The mean resting ejection fraction in patients with previous infarction (48 (10)% was lower

Figure 1 Changes in mean (SD) ejection fraction before and after successful angioplasty and at long term follow up.



than group 1 patients and fell significantly to 40 (16)% (p < 0·001) on exercise. The resting ejection fraction rose to 52 (9)% after successful angioplasty but this change was not statistically significant. The mean exercise ejection fraction after angioplasty was 53% (13), which was significantly higher than the value before angioplasty (p < 0·001). The mean wall motion score before angioplasty was 2·3 (1·9) at rest and 3·3 (2·4) on exercise. The exercise score was significantly improved after angioplasty (1·8 (1·1) (p < 0·005)). There was a fall in resting wall motion score that did not achieve statistical significance (1·8 (1·6)).

At long term follow up the mean resting ejection fraction in these patients was 49 (7%) and the mean exercise ejection fraction was 51 (10)%. Mean wall motion score at rest was 0·9 (0·9) and 1·2 (0·9) on exercise.

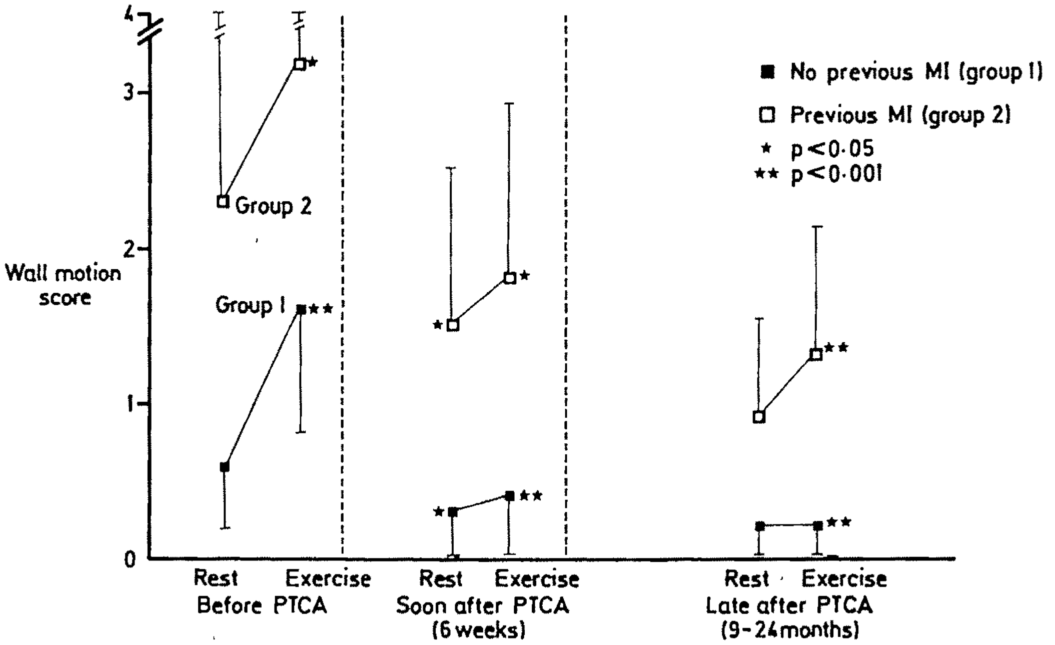
Discussion

Though there have been various studies of the effect of percutaneous transluminal coronary angioplasty on left ventricular function in the short term[7-9] there are few data on long term follow up. In addition, these studies did not specifically examine different subsets of patients with differing degrees of impairment of left ventricular function.

Our study confirms the findings of others that successful angioplasty improves left ventricular function during exercise at early follow up but has little effect on values at rest. As expected, patients with previous myocardial infarction had lower resting ejection fractions, higher wall motion scores, and their change on exercise before angioplasty was more striking than in patients with angina only.

In group 2 there was a modest improvement in resting ejection fraction and wall motion score after angioplasty. There were, however, wide individual variations so as a group these changes were not statistically significant. It may be that in the patients who did show an improvement a component of their resting dysfunction was the result of "hibernating" myocardium at rest caused by a compromised coronary circulation with reduced metabolic activity of some still viable myocardium.[10 11]

Figure 2 Changes in mean (SD) wall motion score before and after successful angioplasty and at long term follow up.



We have previously reported a case of substantial improvement in left ventricular function at rest and on exercise in a patient after successful dilatation of a severe subtotal left anterior descending stenosis.[12] The peak exercise ejection fraction and wall motion score after angioplasty were significantly improved in group 2 patients but the exercise response was still abnormal. In patients with no previous myocardial infarction (group 1) resting function did not improve but after a successful procedure the response to exercise was normal.

The principal findings of this study are that the short term improvement in left ventricular ejection fraction and wall motion score in both groups of patients was maintained at least 9–24 months later. Clearly these are selected patients who have no symptoms suggesting restenosis. Without routine repeat angiographic studies it is possible that some of the study patients had a degree of restenosis in the absence of symptoms. It has been shown that 4% of symptom free patients have angiographic evidence of restenosis.[13] This may account for the slightly lower mean resting ejection fraction in the group without infarction. Five patients, two in group 1 and three in group 2, showed a significantly abnormal exercise response at long term follow up but they had also shown an abnormal response at six week follow up. All five had repeat angiography on the basis of the technetium scan despite the absence of symptoms but none showed angiographic evidence of restenosis. Radionuclide ventriculography at rest and on exercise was used to identify patients with restenosis but the predictive value of the test in all patients, with and without symptoms, was 73%.[14]

In the patients with previous myocardial infarction the tendency towards an improved wall motion score continued beyond six weeks. This may be due to long term improved perfusion of previously hibernating myocardium but the results from this study are not conclusive. Evaluation of the changes in wall motion in a single projection should be viewed with caution; the change was small and did not reach statistical significance. It is encouraging that these patients with compromised left ventricular function did not deteriorate in the long term.

After successful coronary angioplasty the improvement in left ventricular ejection fraction and wall motion score, as assessed by radionuclide studies at rest and on exercise, was maintained at a mean long term follow up period of 15 months. This was true both of patients with previous infarction and of those without. In patients with infarction resting function was abnormal. Long term clinical success at angioplasty was paralleled by long term functional improvement in these indices of left ventricular function.

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Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure

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Abstract

Minute ventilation, respiratory rate, and metabolic gas exchange were measured continuously during maximal symptom limited treadmill exercise in 30 patients with stable chronic heart failure. The ventilatory response to exercise was assessed by calculation of the slope of the relation between minute ventilation and rate of carbon dioxide production. There was a close correlation between the severity of heart failure, determined as the maximal rate of oxygen consumption, and the ventilatory response to exercise. Reanalysis of the data after correction for ventilation of anatomical dead space did not significantly weaken the correlation but reduced the slope of the relation by approximately one third. These results show that the increased ventilatory response to exercise in patients with chronic heart failure is largely caused by mechanisms other than increased ventilation of anatomical dead space. This finding supports the concept that a significant pulmonary ventilation/perfusion mismatch develops in patients with chronic heart failure and suggests that the magnitude of this abnormality is directly related to the severity of chronic heart failure.

Patients with chronic heart failure show an increased ventilatory response to exercise.[1-3] The size of this abnormality is related to the severity of chronic heart failure.[3,4] It has also been established that patients with uncomplicated chronic heart failure maintain essentially normal arterial blood gas concentrations, both at rest and during exercise.[5-7] Consequently the increased ventilatory response that accompanies exercise is hyperpnoea and not hyperventilation, because hyperventilation, by definition, would cause a fall in the arterial concentration of carbon dioxide.

The mechanisms responsible for exercise hyperpnoea in patients with chronic heart failure are poorly understood. Commonly the hyperpnoea is attributed to an increased ventilation of anatomical dead space secondary to an altered relation between tidal volume and respiratory rate.[3] This greater dependence on increasing respiratory rate rather than on tidal volume during exercise in patients with chronic heart failure is claimed to minimise respiratory work in the presence of "stiff" lungs. Recently, it has been suggested that an additional cause of hyperpnoea is an increase in physiological dead space[5-8] secondary to a ventilation/perfusion mismatch [8] The aims of the present study were, first, to determine the relative contributions of these two mechanisms to the measured ventilatory response during exercise in patients with chronic heart failure; and, second, to relate the measured ventilatory response during exercise to the maximum rate of oxygen consumption where the maximum rate of oxygen consumption was regarded as an indicator of the severity of heart failure.

Patients and methods

We studied 30 patients (mean age 53 years (range 30–69); 28 men) with stable chronic heart failure. Heart failure was caused by ischaemic heart disease in 19, by dilated cardiomyopathy in eight, and followed replacement of the aortic valve in three. All patients had been in heart failure for more than 6 months. No patient had had an acute coronary event in the preceding three months. All patients were in sinus rhythm. All were being treated with diuretics and none was receiving β antagonists. No patient had signs or symptoms suggestive of primary lung disease; formal respiratory function tests were not performed.

Exercise testing was performed according to the standard Bruce protocol with the addition of a stage 0 (1 mph (1·6 km/h) at 5% gradient). The exercise laboratory was air conditioned with room temperature maintained in the range 20–21°C. All patients were familiar with treadmill exercise and measurement of respiratory gas exchange. Patients continued their normal medication on the day of exercise testing, and all tests were performed at least three hours after meals.

Minute ventilation, the rate of oxygen consumption, and the rate of carbon dioxide production were measured continuously by the method of Davies and Denison.[9] Validation and reproducibility of this method in our laboratory have been detailed in an earlier paper.[10] In brief, patients were required to breathe through a two way respiratory valve (Collins) held by an adjustable head support. The expiratory port was connected via flexible tubing to a 7 l mixing box (Airspec). Argon was added to the inlet port of the mixing box at a constant flow rate. After full mixing the resultant gas mixture was continuously analysed by a mass spectrometer (Airspec 20MGE). The analogue output from the mass spectrometer was fed to the analogue to digital input channels of a microcomputer (BBC model B). Analogue to digital conversions were performed every 200 ms for each of the four channels (nitrogen, oxygen, carbon dioxide, and argon). Every 30 s a mean value for each channel was calculated, and from these mean values minute ventilation, the rate of oxygen consumption, and the rate of carbon dioxide production were derived. Values were corrected for atmospheric pressure, laboratory temperature, water vapour pressure, and body weight. We calculated the rate of oxygen consumption in ml/min/kg at standard temperature and pressure (dry) (STPD), the rate of carbon dioxide production in ml/min/kg STPD, and minute ventilation as l/min at body temperature, pressure, and saturation (BTPS).

The respiratory rate was determined from a continuous recording of the temperature variation at the mouth obtained from a thermistor mounted inside the respiratory valve. Computation of minute ventilation was corrected for the dead space of the two way respiratory valve (98 ml).

Anatomical dead space was calculated for each patient using the formula:
Anatomical dead space = weight × 2·2 + age where weight and age are measured in kilograms and years respectively.[11]

Patients were encouraged to exercise until symptoms were intolerable. After each exercise test the ventilatory response to exercise was calculated. The total ventilatory response was determined as the slope of the relation between minute ventilation and the rate of carbon dioxide production. The alveolar ventilatory response was determined as the slope of the relation between alveolar ventilation (minute ventilation less the product of anatomical dead space and respiratory rate) and the rate of carbon dioxide production. Both values were obtained by the method of least squares linear regression.

The maximal rate of oxygen consumption ($\dot{V}O_2$ max) was defined as the rate of oxygen consumption at peak exercise.

Results

All exercise tests were performed without complication. The limiting symptom in all patients was breathlessness. $\dot{V}O_2$ max ranged from 8·7 mg/kg/min to 19·1 ml/kg/min indicating moderate to severe heart failure. The relation between minute ventilation and the rate of carbon dioxide production was linear in all patients by visual inspection and the correlation coefficient was r = 0·98 (0·04) mean (SD). Figure 1 shows the raw data obtained from three patients. The last few points in the patient with the steepest slope in figure 1 do deviate from a linear relation. There is scatter of the last points in the other two patients illustrated. These small deviations from linearity do not materially affect the correlation coefficient or the calculation of the slope. The slope of the relation between minute ventilation and the rate of carbon dioxide production (total ventilatory response) was related to the severity of chronic heart failure. Figure 2 shows the relation between $\dot{V}O_2$ max and total ventilatory response for all patients ($r = 0·86$, slope $= -0·32$, $p < 0·001$). Figure 3 shows the relation between $\dot{V}O_2$ max and alveolar ventilatory response ($r = 0·85$, slope $= -0·21$, $p < 0·001$).

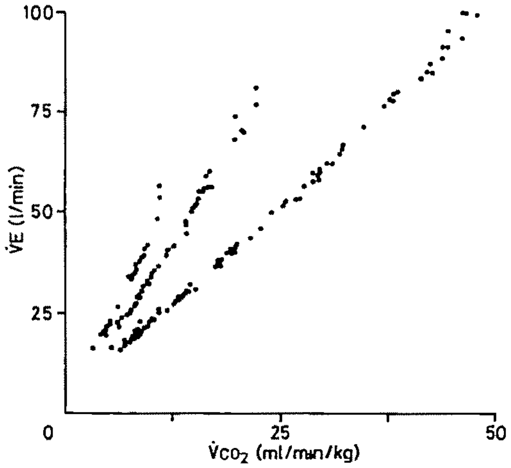

Figure 1 Example of the relation between minute ventilation and the rate of carbon dioxide production for three patients with chronic heart failure of differing severity.

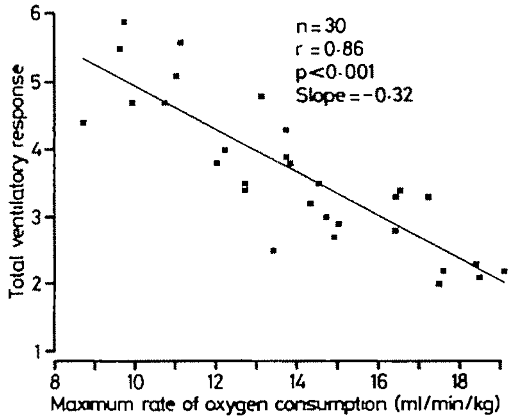

Figure 2 Relation between the total ventilatory response to exercise and the severity of chronic heart failure (measured as $\dot{V}O_2$ max) for all 30 patients.

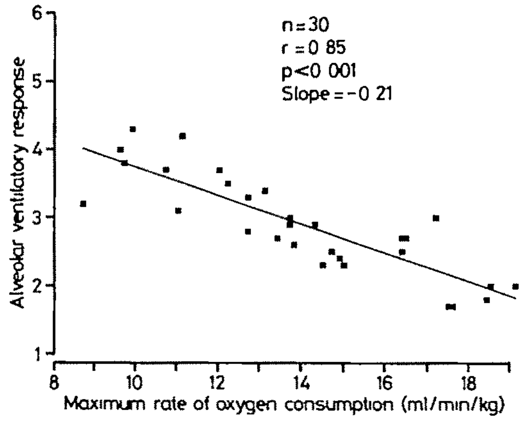

Figure 3 Relation between the alveolar ventilatory response to exercise and the severity of chronic heart failure (measured as $\dot{V}O_2$ max) for all 30 patients.

Discussion

Our results show that in patients with heart failure the relation between total minute ventilation and the rate of carbon dioxide production is almost linear (fig 1). The slope of this relation is inversely related to the peak oxygen consumption on exercise (fig 2). There is a similar but less steep relation between peak oxygen consumption and the slope of the relation between alveolar ventilation and carbon dioxide production (fig 3).

The measurement of $\dot{V}O_2$ max is now well established as an objective and reproducible index of the limitation of exercise capacity in patients with chronic heart failure and is a measure of the severity of heart failure.[10] Thus the ventilatory response to exercise is also an indicator of the severity of heart failure. The only previous study to show such a correlation in individual patients was that of Fink *et al.*[4] They studied bicycle exercise and found an inverse correlation ($r = -0{\cdot}59$, $p < 0{\cdot}01$) between $\dot{V}O_2$ max and a derived value of minute ventilation at a rate of carbon dioxide production of 1 l/min. The higher correlation coefficient in the present study ($r = -0{\cdot}86$, $p < 0{\cdot}001$) may reflect chance variation or, alternatively, may result from the use of treadmill rather than bicycle exercise. Bicycle exercise is associated with lower values for $\dot{V}O_2$ max[12] and a frequent limiting symptom of fatigue rather than breathlessness.[4] Indeed, Wilson *et al* in a more recent study conclude that "bicycle exercise cannot be used to measure $\dot{V}O_2$ max".[12]

With regard to the mechanisms of exercise hyperpnoea in patients with chronic heart failure, our results show that correction for ventilation of anatomical dead space only reduced the gradient of the relation between ventilatory response and $\dot{V}O_2$ max by approximately one third. In consequence, we conclude that an altered respiratory pattern in patients with severe chronic heart failure only accounts for approximately one third of the increased exercise hyperpnoea seen in patients with heart failure (compare, for example, ventilatory response at a maximum rate of oxygen consumption of 10 ml/min/kg in figs 2 and 3). Arterial blood gas tensions were not measured, but, assuming these remained constant,[5–7] the results must also imply that approximately two thirds of the exercise hyperpnoea is due to an increased physiological dead space, and consequently a significant ventilation/perfusion mismatch. Our results further indicate that the magnitude of this abnormality is directly related to the severity of chronic heart failure as assessed by peak oxygen consumption on exercise.[10]

As in earlier studies[3,4] we found a close linear correlation between minute ventilation and the rate of carbon dioxide production during exercise in patients with chronic heart failure. The demonstration that the slope of this relation in individual patients was closely related to the severity of chronic heart failure suggests the possibility that this measurement may provide a simple and objective measure of severity of chronic heart failure. This measurement can be obtained without the patient being required to perform maximal exercise. A consequence is that obtaining the measurement is less unpleasant to the patient and not dependent on encouragement of the patient in the last few moments of an exercise test. The measurement is ideally suited to repeated evaluation.

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Post-extrasystolic potentiation without a compensatory pause in normal and diseased hearts

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Abstract

Variables derived from left ventricular volume were used to study post-extrasystolic potentiation. Left ventriculograms were obtained from 11 healthy individuals and 49 patients with coronary heart disease (30 with a previous myocardial infarction and 19 without any signs of myocardial damage). Post-extrasystolic potentiation was induced by a regularly driven right atrial rhythm that was interrupted by one atrial extrasystole in such a way that the post-extrasystolic RR interval was kept equal to the basic RR interval. The left ventricular end diastolic volumes of the pre-extrasystolic and post-extrasystolic beats were equal. In all groups there was evidence of post-extrasystolic potentiation in one or more of the indices of left ventricular function (ejection fraction, mean normalised systolic ejection rate, end systolic volume, and stroke volume). Potentiation was especially evident in patients with left ventricular damage; this suggests that a compensating mechanism is an intrinsic property of the myocardium.

The Frank-Starling mechanism does not contribute to the increased performance of the post-extrasystolic beat in normal individuals or in patients with coronary artery disease.

A century ago Langendorff found that the force of contraction was stronger in the beat that followed an extrasystole.[1] Hoffman *et al* called this phenomenon post-extrasystolic potentiation.[2] Cohn in an editorial cited several investigators[3] and attributed post-extrasystolic potentiation in vivo to the prolonged pause that follows the extrasystole, which would lead to increased ventricular filling,[4-6] and reduced aortic impedance (resulting from a decline in aortic pressure during that compensatory pause).[7] A third mechanism, which was seldom taken into account, is the phenomenon called "rest contraction".[8-10] This phenomenon, which is part of the so-called restitution curve,[11] is present after a compensatory pause.

Sung *et al* showed post-extrasystolic potentiation in healthy individuals without an increased end diastolic volume as a contributing factor.[12] Wisenbaugh *et al* found evidence of post-extrasystolic potentiation without an increased post-extrasystolic end diastolic volume in patients with volume overload caused by chronic valve regurgitation.[13] In these studies the consequence of the compensatory pause—that is the effect of the "rest contraction"—on the size of the post-extrasystolic beat was not taken into account.

Van der Werf *et al* showed that human post-extrasystolic potentiation can be elicited without a compensatory pause.[14] They provoked controlled post-extrasystolic potentiation by altering the RR interval and by use of pressure-derived indices of contractility in normal and diseased hearts.

We used volume derived indices to investigate post-extrasystolic potentiation after a post-extrasystolic RR interval without a compensatory pause in healthy individuals and in patients with coronary heart disease.

Patients and methods

PATIENTS

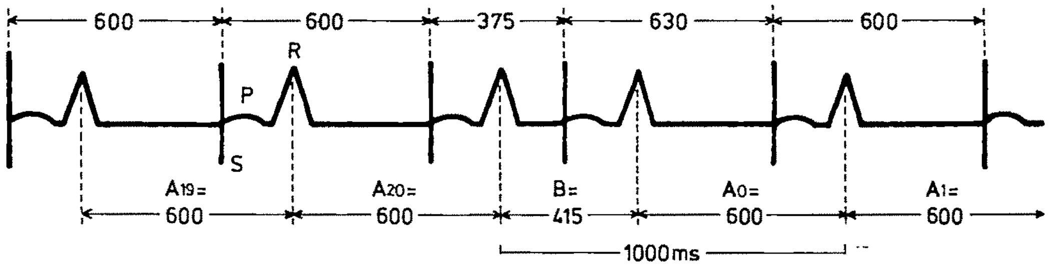
We studied 60 patients. Each patient gave informed consent. The patients were divided into three groups: 11 with atypical chest pain, normal coronary arteries, and normal left ventricular pressure and volumes (group 1); 19 patients with typical angina pectoris without evidence of previous myocardial infarction (group 2); and 30 patients with enzymatic and electrocardiographic evidence of an earlier transmural myocardial infarction (group 3). We excluded patients with other forms of cardiac disease and patients who had had cardiac surgery.

STIMULATION PROCEDURE

We used a computed controlled stimulator to ensure that the duration of the post-extrasystolic RR interval was equal to the basic RR interval.[14] The stimulation pattern was applied to the right atrium in such a way that variations in atrioventricular nodal delay caused by changes in the extrasystolic PR interval were compensated for. A test series of atrial stimulation pulses was generated and RR intervals were measured on line by computer. PR intervals were measured and atrial stimulus intervals were corrected by iteration so that the length of the post-extrasystolic RR interval was equal (inaccuracy < 1%) to that of the pre-extrasystolic cardiac cycle (figure). A stimulation series consisted of 20 basic intervals interrupted by one extrasystolic interval. The post-extrasystolic beat (P) was compared with the pre-extrasystolic or control beat (C).

QUANTITATIVE LEFT VENTRICULOGRAPHY

Left ventriculography (50 frames) was



Schematic presentation of the stimulation procedure used Time intervals between stimulation spikes (S), P waves, and R waves are shown in ms After 20 basic stimuli a shorter stimulus-stimulus interval (375 ms) was applied resulting in an RR interval of 415 ms (B) The difference between the RR interval and the stimulus-stimulus interval is caused by prolongation of the PR interval preceding the extrasystole To correct for this prolongation, the post-extrasystolic stimulus-stimulus interval was chosen in such a way (630 ms) that it results in a post-extrasystolic RR interval (A 0) equal to the basic interval (A 20)

performed in the frontal and left lateral projection after injection of 40–56 ml metrizoate (Isopaque). The pulse for each cineframe was recorded on paper together with the electrocardiogram. We chose the peak of the R wave to mark end diastole. End systole was more difficult to identify, particularly in patients with coronary heart disease.[15] The frame taken 80 ms before the opening of the mitral valve was taken as end systole. The end diastolic and end systolic ventricular silhouettes were traced by hand and biplane left ventricular volumes were calculated by Dodge's area-length method.[16] Stroke volume, ejection fraction, and mean normalised systolic ejection rate were calculated from the volumes. The ejection rate was calculated by dividing the stroke volume by the duration of the ejection period. Because Van der Werf *et al* found no significant difference in end diastolic aortic pressure between pre-extrasystolic and post-extrasystolic beats, using an identical stimulation protocol,[14] we did not measure aortic pressures in our study. Data are presented as mean (SD).

We used the Wilcoxon matched pairs signed ranked method for statistical analysis. Differences between groups were regarded as significant when p was $<0{\cdot}05$.

INTRA-OBSERVER VARIABILITY

End diastolic and end systolic volumes were calculated twice by the same investigator at an interval of about 3 months (table 1). The degree of intra-observer variability was affected by the stage (end diastolic or end systolic) at which the volume was measured. Nevertheless, the first and second determination at both end systole and diastole were not statistically different (Student's paired *t* test) (p < 0 05).

Results

Table 2 shows the calculated ventricular volumes and derived functional indices in the three groups of patients. There was no statistically significant difference between the left ventricular end diastolic volume of the post-extrasystolic (P) beat and the control (C) beat in all three groups. The only pre-extrasystolic values that were significantly different from those in the controls were the increased end diastolic and end systolic volumes and decreased ejection fraction found in group 3.

Although the end diastolic volume preceding the post-extrasystolic beat was unchanged and the contribution of a compensatory pause was excluded, several indices of left ventricular function indicated enhanced performance of

Table 1 Intra-observer variability of end diastolic and end systolic volumes measured twice by the same investigator at an interval of 3 months

					Coefficients of	
Volume	*n*	*Mean*	*Difference**	*SD*	*Correlation (r)*	*Variation (%)†*
End diastolic	53	77	0 53	5 4	0 98	7
End systolic	36	42	0 94	7 1	0 96	17

*Mean difference between the first and the second determinations

† $\frac{\text{SD}}{\text{mean}} \times 100\%$

The first and second determinations of end diastolic and end systolic volumes were not significantly different

Table 2 Mean (1 SD) calculated ventricular volumes and derived functional indices

	Group 1 (n = 11)		*Group 2 (n = 19)*		*Group 3 (n = 30)*		
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*p*
Ejection fraction	0 64 (0 10)	0 66 (0 10) p < 0 05	0 64 (0 10)	0 66 (0 13)	0 46 (0 12)	0 52 (0 13)	<0 05
MNSER	147 (35)	150 (38)	155 (39)	164 (44) p < 0 05	142 (44)	166 (65)	<0 05
End systolic volume	24 (8)	23 (9)	25 (12)	24 (14)	51 (23)	45 (22)	<0 05
Stroke volume	40 (6)	42 (6) p < 0 05	43 (9)	45 (10)	40 (11)	46 (14)	<0 05
End diastolic volume	64 (8)	66 (9)	68 (17)	69 (17)	91 (24)	91 (26)	
Basic interval (ms)	754 (60)		734 (58)		750 (78)		
Extrasystolic interval (ms)	546 (81)		533 (71)		559 (76)		
$\frac{\text{Extrasystolic}}{\text{basic}} \times 100$	72 (5)		72 (6)		75 (7)		
Age (yr)	50 0 (8)		52 4 (7)		50 9 (10)		

MNSER, mean normalised systolic ejection rate.
There was strong evidence of potentiation in all four systolic variables in the group of patients with documented transmural myocardial infarction (group 3).

that beat (table 2). In the post-extrasystolic beat the end systolic volume was decreased; ejection fraction, mean normalised ejection rate, and stroke volume were increased significantly in group 3. Thus the degree of potentiation was greatest in the group with pre-existing left ventricular dysfunction. In contrast, the potentiation effects in groups 1 and 2 were slight or absent (table 2).

Discussion

We found that volume derived variables indicated little or no post-extrasystolic potentiation of left ventricular performance in controls and in patients with coronary heart disease without myocardial infarction. In these two groups only one of the three indices of left ventricular performance indicated the presence of post-extrasystolic potentiation. In patients with previous myocardial infarction, however, potentiation was evident in all the measured indices and reference values for left ventricular function were abnormal (table 2). This potentiation was independent of preload—as it was in healthy individuals in an earlier study[12] and in animals.[17] Potentiation may be attributed to an increased contractile reserve in non-infarcted areas, which compensates for the loss of contractile power in the infarcted myocardium. Van der Werf *et al* reported post-extrasystolic potentiation of the left ventricular performance when they used the same stimulation protocol in healthy individuals and in patients with coronary heart disease without infarction.[14] They were studying pressure derived variables, and they too found no significant difference between the preloads of the post-extrasystolic beats and the pre-extrasystolic beats.

In most studies[18–20] the contribution of the prolonged pause after an extrasystole to the enhanced myocardial contractile performance was attributed to an increase in end diastolic volume and an increase in the active state mediated by calcium.[21] These two effects were avoided in the present study by preventing augmented diastolic filling and by keeping the post-extrasystolic interval equal to the basic interval. So the Frank-Starling mechanism[22] and/or "rest contraction"[8–10] do not necessarily participate in or contribute to the increase of the post-extrasystolic contraction.

The role of the compensatory pause and its contribution as part of the interval-force relation to the increased performance of the post-extrasystolic beat has been overlooked by many investigators of post-extrasystolic potentiation.[4 5 12 13 18–20 23 24] In these studies the so-called post-extrasystolic beat is a beat potentiated by the prepreceding shorter interval and at the same time augmented by the longer interval that immediately preceded it.[8] Sung *et al* showed post-extrasystolic potentiation with a compensatory pause in healthy individuals—as in our study without an increased left ventricular volume.[12] Comparison of the results of this study with ours emphasises the contribution of the prolonged pause after the extrasystole to the increase in the force of the post-extrasystolic beat.

Our study of volume derived indices showed that post-extrasystolic potentiation of the left ventricle did not depend on the preload. Our results suggest that the Frank-Starling mechanism is not involved in post-extrasystolic potentiation in normal and diseased human hearts.

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Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass

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Abstract

Two families are described in which individuals showed widespread myocardial disarray at histological examination, in the absence of macroscopic cardiac hypertrophy. In one family the clinical presentation was that of sudden unexpected cardiac death in four family members; members of the other family presented with electrocardiographic repolarisation changes and abnormalities of left ventricular diastolic function.

The finding of myocardial disarray, the characteristic histological abnormality of hypertrophic cardiomyopathy, in the absence of increased cardiac mass suggests a wider range of abnormality in hypertrophic cardiomyopathy than is currently recognised.

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The most characteristic abnormalities of hypertrophic cardiomyopathy are an increase in ventricular muscle mass with myocyte hypertrophy and disarray.[1-3] The criteria for the diagnosis of hypertrophic cardiomyopathy and the nomenclature for its description have expanded since Teare's original description of these abnormal features.[1-4]

In the 1960s the diagnosis relied on clinical and haemodynamic features of a left ventricular outflow tract pressure drop (hypertrophic obstructive cardiomyopathy, idiopathic hypertrophic subaortic stenosis, muscular subaortic stenosis)[2 3 5]; it is now known that only about 35% of patients have left ventricular outflow tract pressure differences at rest.[6] The development of M mode echocardiography in the 1970s permitted the visualisation of the interventricular septum and the posterior left ventricular wall at mitral valve level.[7 8] M mode echocardiography confirmed earlier observations and led to the assertion that asymmetrical septal hypertrophy was the pathognomonic feature of the condition.[9] Asymmetrical septal hypertrophy is seen in 60–70% of patients with hypertrophic cardiomyopathy but it is also found in other patient groups.[10] Currently the clinical diagnosis of hypertrophic cardiomypathy is based on the demonstration of unexplained left ventricular hypertrophy when the entire heart is visualised by cross sectional echocardiography.[11 12]

The extent of myocyte disarray is now regarded as a specific histological marker of hypertrophic cardiomyopathy. In normal hearts the mean proportion of the septum with disarray is 1·5%; in hypertrophic cardiomyopathy disarray is found in 30% of the total tissue area.[13 14] The histological appearances of disarray are classified as type I—in which the myocytes are predominantly cut longitudinally—and type II—in which the myocytes are cut transversely. The degree of disarray on histological slides is expressed as a proportion of the total area cut longitudinally or transversely, and the largest percentage is used to indicate the amount of disarray.[13 14]

We report two families with myocyte disarray but no increase in cardiac mass. These families raise questions about the appropriateness of current nomenclature and highlight potential limitations of current diagnostic criteria.

Clinical and pathological details

FAMILY A

This family came to attention because of a strong history of premature sudden death. The proband (case 1) died at the age of 38 years with no previous history of cardiac disease. Her daughter (case 2), sister (case 3), and nephew (case 4) (aged 21, 42, and 17 years respectively) also died suddenly and unexpectedly without any previous history to suggest cardiac abnormality (fig 1).

Necropsy was performed on all 4. Table 1 gives detailed pathological information. The macroscopic appearances of the hearts were normal. Heart weights were not increased; cavity size and ventricular wall thickness were normal. Histological assessment, however, showed widespread interstitial fibrosis with

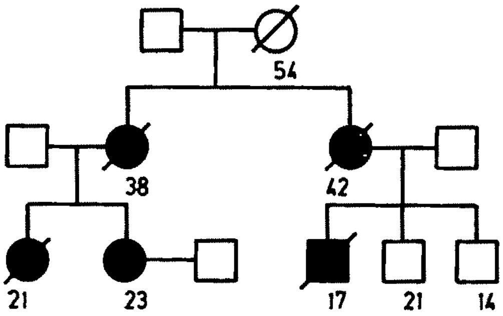

Figure 1 Pedigree of family A. Solid symbols represent affected individuals Age at death or diagnosis is shown.

Table 1 Results of pathological examination in five individuals showing considerable myocardial disarray

Patient	*Age/sex*	*Cause of death*	*Heart weight (g)*	*LV mass (g)*	*RV mass (g)*	*Disarray (%)*
Family A						
1	38/F	SCD	374	—	—	61·3
2	21/F	SCD	292	136	42	32·8
3	42/F	SCD	—	—	—	36·0
4	17/M	SCD	341	163	47	47·0
Family B						
5	44/F	MI	325	164	44	25·6

LV, left ventricular, MI, myocardial infarction, RV, right ventricular, SCD, sudden cardiac death

type I disarray in three (myocytes predominantly cut longitudinally). In patient 3 there was diffuse fibrosis with 36% disarray on transverse section (type II) in the only tissue sample available for review from the original necropsy (fig 2).

The three surviving first degree relatives were symptom free. Two were willing to be assessed. Clinical examination was normal in both, and in one the electrocardiogram and cross sectional echocardiogram were also normal. In the surviving daughter (case 6) of the proband, however, the resting electrocardiogram was abnormal, and fulfilled voltage criteria for left ventricular hypertrophy, with associated widespread abnormalities of repolarisation. This woman provides an opportunity to study her family's cardiac abnormality in life. Her cross sectional echocardiogram showed normal cavity size, wall thickness, and functional indices (left ventricular end systolic dimension 26 mm, left ventricular end diastolic dimension 40 mm, interventricular septal thickness 9 mm, posterior left ventricular wall thickness 9 mm) (fig 3). She exercised for 12 minutes of a standard Bruce protocol; her heart rate increased from 60 to 167 beats/min, with maximal oxygen consumption ($\dot{V}O_2$ max) of 40 ml/kg/min (100% of her predicted maximum). The T wave inversion in the anterior chest leads of the resting electrocardiogram became normal during exercise. The blood pressure response to exercise, however, was abnormal; the resting systolic pressure was 100 mm Hg, it rose early during exercise to 125 mm Hg, and fell to 90 mm Hg at peak exertion. The control of the peripheral vasculature, investigated by forearm plethysmography during supine bicycle exercise, was abnormal with an increase in forearm blood flow indicating inappropriate and generalised vasodilatation. A high gain signal averaged electrocardiogram did not show late potentials and there were no arrhythmias during repeated 48 hour electrocardiographic monitoring. The findings on left and right cardiac catheterisation (including filling pressures) were normal and there was no resting or inducible outflow tract gradient in the left or right ventricle. At electrophysiological study the basic conduction intervals were normal and there was no evidence of an accessory atrioventricular pathway or of accelerated atrioventricular nodal conduction. Atrial vulnerability was assessed by high rate burst pacing and extrastimuli, and ventricular vulnerability by programmed stimulation to stage 8 of the Wellens protocol (drive cycle 420 ms and 2 extrastimuli), but tachycardia was not initiated.

She was treated with low dose amiodarone (200 mg daily, plasma concentration 0·8 mg/l), and has remained well during four years of follow up.

FAMILY B

In this family the proband (case 5) died of

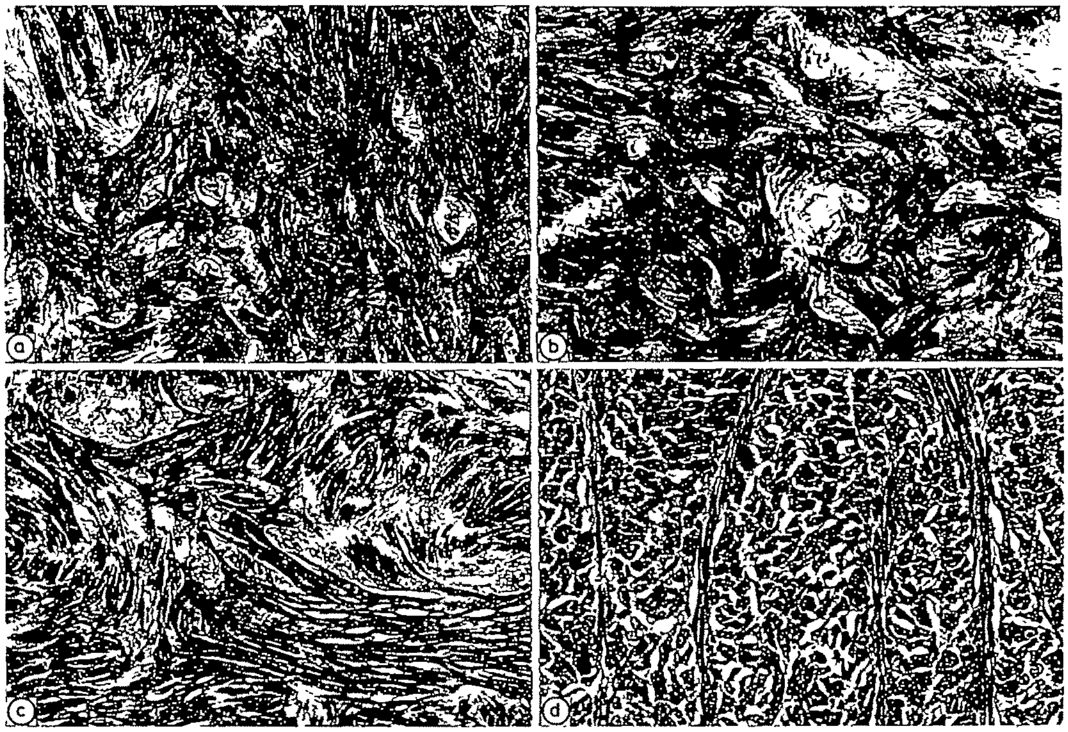

Figure 2 (a) Disorganisation of cardiac muscle cells that are aligned obliquely (type I) to each other forming tangled masses (case 1). (b) Disorganisation showing whorled arrangement (type I) of cardiac muscle cells around a central focus of connective tissue (case 1) (c) Disorganisation in which bundles of cardiac muscle cells are arranged at oblique angles (type I) (case 2) (d) Disorganisation with narrow bands of longitudinally (type II) arranged myocytes alternating with transversely cut myocytes (case 3).

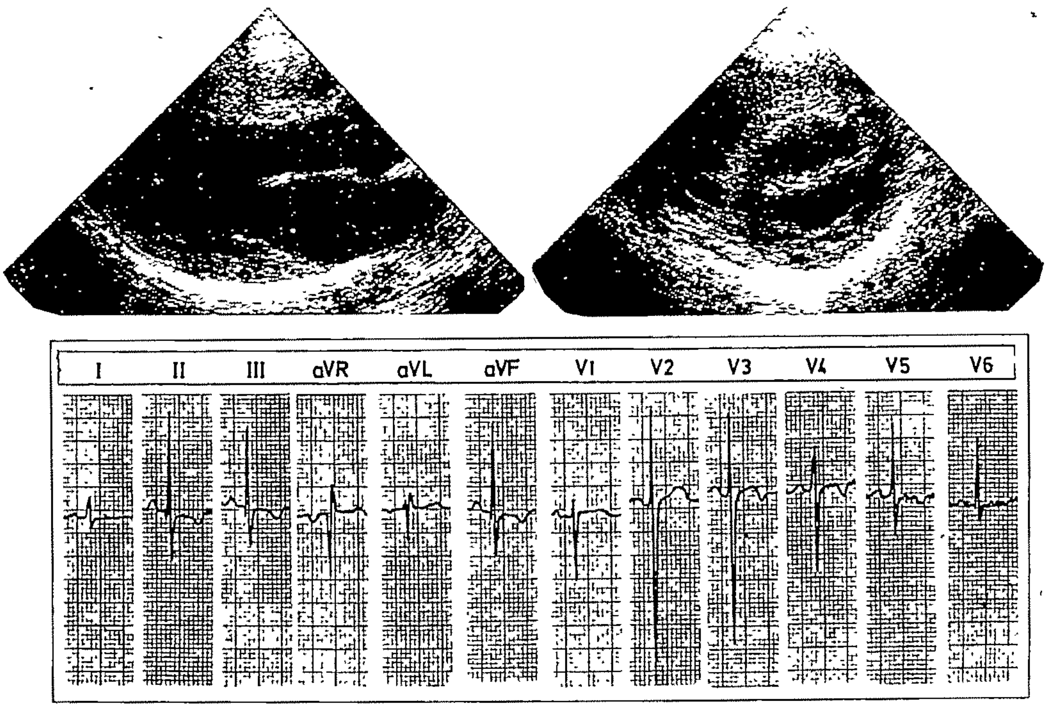

Figure 3 Cross sectional echocardiogram and 12 lead surface electrocardiogram of case 6 (family A)

myocardial infarction after coronary arteriography in 1979. She had a 5 year history of paroxysmal atrial fibrillation and an abnormal resting electrocardiogram showing atrial overload, voltage criteria of left ventricular hypertrophy, and widespread repolarisation abnormalities Six months before her death she started to complain of chest tightness and dyspnoea on exertion, which were relieved by rest and sublingual glyceryl trinitrate. M mode echocardiography at that time showed a small left ventricle (end diastolic dimension 41 mm, end systolic 29 mm) with wall thickness at the upper limit of normal (interventricular septum 12 mm, posterior left ventricular wall 13 mm), and a restrictive filling pattern. The left atrial dimension was also at the upper limit of normal (40 mm). Left ventricular cineangiography showed normal systolic function and coronary arteriography showed some irregularity of the left main stem coronary artery. During the next 6 months she had progressive angina despite treatment with propranolol, nitrates, and verapamil. At restudy when the right coronary arteriogram was performed (before cannulation of the left coronary artery) the entire left coronary system was seen to fill retrogradely. After this she suffered an extensive anterior myocardial infarct and died 24 hours later in cardiogenic shock.

The clinical diagnosis was severe stenosis of the left main stem coronary artery. At necropsy a small plaque of coronary atheroma was found in the proximal left main stem coronary artery; there was no significant atheroma elsewhere in the coronary tree. The infarct that caused her death was assumed to have been caused by spasm at the site of the plaque in her left main coronary artery. Otherwise the heart was macroscopically normal, apart from unusual rigidity of the atria, and weighed 325 g (normal for her body weight). Histological examination showed extensive interstitial fibrosis of the atria with obliteration of the sinoatrial node. The ventricular myocardium showed less pronounced fibrotic changes but severe myocyte disarray (25·6% type I).

Eight first degree relatives of this patient, all of whom were symptom free, were assessed (fig 4). Four had abnormal electrocardiograms and cross sectional echocardiograms. All four showed abnormalities of ventricular repolarisation on the resting 12 lead electrocardiogram; atrial fibrillation was also seen in one, and left or right atrial overload or both was seen in the other three. The echocardiograms in these four patients showed normal heart size, ventricular cavity dimensions, and ventricular wall thickness. The ventricular filling patterns, however, showed a phase of early rapid filling that stopped abruptly in mid-diastole. In addition, the echocardiogram confirmed the presence of atrial enlargement in three of these four (table 2).

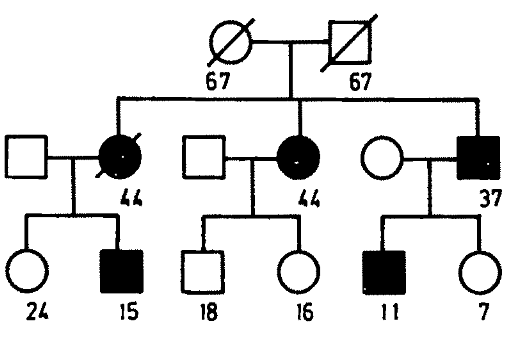

Figure 4 Pedigree of family B Solid symbols represent affected individuals. Age at death or diagnosis is shown.

Discussion

Familial hypertrophic cardiomyopathy shows a mendelian autosomal dominant pattern of inheritance.[15] The pattern of inheritance in the two families described is consistent with autosomal dominance—if one accepts that the survivors with electrocardiographic or echocardiographic abnormalities or both have the same condition as those examined at necropsy.

Table 2 *Clinical details of surviving family members*

		Electrocardiogram						*Echocardiogram*				
Patient	*Age/sex*	*Rhythm*	*RA+*	*LA+*	*T abn*	*ST abn*	*LVH*	*LVWT (mm)*	*LVED (mm)*	*LVES (mm)*	*LA (mm)*	*EF (%)*
Family A												
6	25/F	SR	—	—	+	—	+	10	35	20	24	63
Family B												
7	15/M	SR	+	—	—	+	+	9	43	26	45	70
8	11/M	SR	+	—	+	—	—	8	40	27	42	68
9	44/F	AF	+	+	—	+	—	10	43	32	46	47
10	37/M	SR	—	+	—	—	+	10	49	33	39	63

Abn, abnormality, AF, atrial fibrillation, EF, ejection fraction, LA, left atrial, LVED, left ventricular end diastolic dimension, LVES, left ventricular end systolic dimension, LVWT, left ventricular wall thickness, RA, right atrial, SR, sinus rhythm

The histological features of hypertrophic cardiomyopathy are characteristic. Myocyte disarray, associated with an excess of loose connective tissue, is quantitatively different in this condition from the appearances seen in other forms of cardiac hypertrophy.[1–3] The disorganised muscle bundles have a characteristic whorled pattern on light microscopy. The histological findings in the patients from these two families were indistinguishable from those found in hypertrophic cardiomyopathy, although none of the typical macroscopic features was present and the heart weights were normal.

One of the possible consequences of myocyte disarray is electrical instability of the myocardium, which allows the development of ventricular fibrillation but does not provide the basis for sustained ventricular tachycardia (this arrhythmia is very rare in hypertrophic cardiomyopathy).[16] The exact mechanism of sudden cardiac death in hypertrophic cardiomyopathy is still unresolved. Based on our studies in this condition, we believe that the primary event is most often haemodynamic collapse resulting from inappropriate circulatory reflexes.[17 18] The resulting hypotension and ischaemia may provoke ventricular fibrillation in individuals with severe disarray. Investigation of the surviving member of family A did not show any evidence of electrical instability but did suggest abnormal control of the circulation during exercise.

Myocyte disarray may also contribute to abnormalities of left ventricular diastolic function seen in hypertrophic cardiomyopathy. In Family B restrictive physiology was seen in surviving family members, although only the proband showed histological proof of myocyte disarray. The explanted hearts of five young patients (age < 15 years) undergoing transplantation for restrictive cardiomyopathy, which were examined recently by us, showed similar histological features (A Pomerance, personal communication).

Did the patients described have hypertrophic cardiomyopathy without hypertrophy? If they do represent a previously unrecognised form of the condition then, by implication, the range of disease recognised by standard diagnostic echocardiographic criteria is limited. More extensive characterisation of similar patients may confirm our impression that hypertrophic cardiomyopathy may exist without hypertrophy or that within a family some affected members may have hypertrophy while others do not. Ultimately, however, accurate diagnosis may require identification of the gene responsible or of a genetic marker that is linked to the gene locus.

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Streptokinase treatment for femoral artery thrombosis after arterial cardiac catheterisation in infants and children

F Brus, M Witsenburg, W J D Hofhuis, J A Hazelzet, J Hess

Abstract

Data on 205 children who underwent retrograde arterial catheterisation were studied to assess the frequency of femoral artery thrombosis and the safety and efficacy of systemic streptokinase treatment for this complication. In 29 (14%) a transarterial balloon dilatation was performed. In 15 (7·3%) patients impaired arterial perfusion due to vascular spasm with or without thrombus formation was seen in the cannulated leg after catheterisation. Despite heparinisation, signs of impaired arterial circulation persisted in nine patients (4·4% of the total). In these patients femoral artery thrombosis was strongly suspected. Six (53%) of these had undergone a balloon dilatation. Therefore in this study the risk of femoral artery thrombosis developing was 12 times greater after transarterial balloon dilatation than after arterial catheterisation without dilatation (20·6% *v* 1·7%). Systemic infusion of streptokinase was started in all patients with femoral artery thrombosis. Arterial perfusion became normal in all patients, though in one this was delayed. Haematological monitoring showed lengthening of the thrombin time and a decrease of the fibrinogen concentration during streptokinase treatment. There were no serious complications.

Systemic infusion of streptokinase is a safe and useful treatment in children with persistent femoral artery thrombosis after arterial cardiac catheterisation.

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Femoral artery thrombosis is the most common complication of retrograde arterial cardiac catheterisation in children.[1-3] Catheterisation of infants weighing less than 10 kg and the growing use of transarterial balloon dilatation procedures increase the frequency of this complication.[2 4 5]

In older children surgical thrombectomy has been undertaken with varying success.[1 4 5] Because the risk of extending vascular damage is higher in neonates and infants they are less suitable for surgical intervention.[2 5]

The systemic use of thrombolytic agents seems to be a safe and effective alternative to surgical treatment.[4 5] We studied a group of children treated with streptokinase because of femoral artery thrombosis after cardiac catheterisation.

Patients and methods

Between 1 January 1987 and 1 December 1988, retrograde arterial cardiac catheterisation was performed in 205 children. Of these, 29 (14%) children underwent transarterial balloon dilatation. These children received an extra intravenous bolus of heparin (110 U/kg) during the procedure as well as the heparin solution used routinely in every child to flush catheters. Thirty four (16%) children weighed less than 10 kg.

Before and after catheterisation the arterial perfusion of both legs was assessed by examination of arterial pulses, blood pressure, colour, and temperature. Patients with absent or reduced arterial pulsations, substantially decreased blood pressure, pallor, and diminished skin temperature of the cannulated leg shortly after the end of the procedure were considered to have impaired arterial perfusion due to arterial spasm with or without thrombus formation. We studied the data on these patients.

In all these patients heparin was administered for different times and monitored by the activated partial thromboplastin time. In patients with persistent signs of impaired arterial circulation despite heparinisation a tentative diagnosis of arterial thrombosis was made and streptokinase was used for systemic thrombolytic treatment.

The distribution of age and weight (mean (SD)) and also the interval (mean (SD)) between the end of the catheterisation and the start of streptokinase treatment were determined. The duration of treatment (mean (SD)) was also assessed.

Before and during streptokinase treatment prothrombin time, activated partial thromboplastin time, and plasma fibrinogen concentrations were recorded in all patients; in some patients the thrombin time was also measured. Two hours after the end of streptokinase treatment heparinisation was restarted in all patients to prevent re-thrombosis after successful treatment or persisting thrombus formation after treatment failure. This was continued for 12 hours.

Results

Shortly after the end of the catheterisation 15 (7·3%) of 205 patients showed impaired arterial perfusion of the cannulated leg. In six (40%) of these the arterial circulation became normal during systemic heparin treatment. Despite continued heparinisation arterial perfusion remained impaired in the remaining nine patients (60%, 4·4% of 205 patients)

Table 1 Patients with femoral artery thrombosis treated by systemic infusion of streptokinase

Patient No	*Age (yr)*	*Weight (kg)*	*Diagnosis*	*Transarterial balloon dilatation*	*Interval between end of catheterisation and start of streptokinase (h)*
1	5·4	17·7	Aortic recoarctation	+	144
2	1·6	8·8	TA	–	51
3	1·2	7·0	VSD	–	48
4	9·6	22·4	AVS	+	48
5	0·4	6·6	AVS	+	122
6	11·0	25·4	AVS	+	24
7	0·08	5·2	AVS	+	24
8	6·6	17·2	MPPS	+	19
9	0·02	3·2	PA, VSD	–	56
Mean (SD)	3·9 (4·3)	12·6 (8·1)			59·7 (44·0)

TA, tricuspid valve atresia; VSD, ventricular septal defect, AVS, aortic valve stenosis, MPPS, multiple peripheral pulmonary stenoses, PA, pulmonary atresia

Table 2 Systemic streptokinase infusion in nine patients with femoral artery thrombosis after retrograde arterial catheterisation

Patient No	*Loading dose in 30 min (U/kg)*	*Infusion dose (U/kg/h)*	*Duration (h)*	*Complications*
1	1000	1000	29	None
2	1000	1000	7	None
3	1000	1000	12	None
4	2000	1000	58	Haematoma groin
5	3000	1500	8	None
6	3000	1000	24	Bleeding groin
7	3000	1000	24*	None
	3000	2000	45	
8	3000	1000	120	None
9	3000	1000	72	No effect

*Because of an inadequate result after 24 hours of treatment the dose of streptokinase was increased after another loading dose. This was successful after 45 hours

59·7 (44·0) hours (range 19–144 hours) after the procedure and femoral artery thrombosis without vascular spasm was strongly suspected (table 1). Six of these nine patients had undergone a transarterial balloon dilatation. The median weight of these children was 12·6 (8·1) kg (range 3·2–25·4 kg); five of them weighed less than 10 kg. The median age was 3·9 (4·3) years (range 9 days–11 years).

During systemic streptokinase treatment (table 2) arterial perfusion became normal in eight (89%) of nine patients after 7–120 hours (mean 39·6 (38·9) hours). Because of persisting impaired perfusion after 24 hours of treatment the streptokinase dose was increased in one patient (patient 7, table 2) after another loading dose. This resulted in normal arterial circulation after 45 hours. In the youngest patient (patient 9, table 2) absence of pulses and low systolic blood pressure persisted despite laboratory signs of adequate fibrinolysis. After 72 hours thrombolytic treatment in this patient was stopped. However, femoral artery perfusion was normal 5 days after the end of streptokinase treatment. There were no signs of re-thrombosis at follow up after 3–20 months in any patient.

Table 3 Thrombin time and plasma fibrinogen concentration before and during streptokinase treatment

	Thrombin time (s)		*Plasma fibrinogen (g/l)*	
Patient No	*Before*	*During*	*Before*	*During*
1	17	28	3·0	2·0
2	19	56	2·6	0·8
3	—	—	2·6	1·0
4	10	26	2·6	1·4
5	19	31	2·3	1·4
6	21	25	2·5	2·6
7	18	25	2·1	1·6
8	21	32	3·8	2·5
9	—	—	3·7	0·8
Mean (SD)	17·9 (3·8)	31·9 (11·0)	2·8 (0·6)	1·6 (0·7)

During streptokinase treatment the prothrombin time and partial thromboplastin time did not change. The thrombin time increased (from 17·9 (3·8) s to 31·9 (11·0) s, mean relative increase of 0·85 (0·61) and the plasma fibrinogen concentration decreased (from 2·8 (0·6) g/l to 1·6 (0·7) g/l, mean relative decrease of 0·42 (0·24)). The fibrinogen concentration did not change in patient 6, in whom streptokinase treatment resulted in a normal circulation after 45 hours (table 3).

There was no substantial bleeding during or after streptokinase treatment except for minimal bleeding at the arterial entry site that could be stopped by groin compression. No allergic reactions were seen.

Discussion

Obstruction of the femoral artery by thrombus is a complication of retrograde arterial catheterisation in children. This has been confirmed by arteriography in some studies.[1-3] Vascular spasm only contributes to femoral artery obstruction shortly after the end of the procedure.[2] Spasm is unlikely to persist for more than a few hours.[2] In this study we regarded persistent signs of impaired arterial circulation despite heparinisation as being the result of thrombus formation without vascular spasm.

Femoral artery thrombosis is the most common complication after retrograde arterial catheterisation in children[1-3]—it was reported in 3–5% of patients despite increased experience with catheterisation techniques, better materials, and systemic treatment with heparin.[1 4 5] The result in our study (4·4%)

accords with these earlier results. Furthermore, femoral artery thrombosis was 12 times more common after retrograde transarterial balloon dilatation than after arterial catheterisation alone (20·6% *v* 1·7%). The larger diameter of the balloon catheters and the irregular surface of the balloon may contribute to increased intimal damage and vascular spasm.[4,6] This is an important finding because the number of retrograde transarterial balloon dilatations has greatly increased in past years.[6–8] Young children, especially those weighing less than 10 kg, have a higher frequency of femoral artery thrombosis after retrograde arterial catheterisation than older children and adults.[2,4,5] We found femoral artery thrombosis in 14·7% of children weighing < 10 kg and in 2·3% of children weighing > 10 kg. Although tissue ischaemia after femoral artery thrombosis is rare, disturbance of growth and function of the leg can be impressive.[2,4,9] Therefore, it is very important to evaluate arterial perfusion of both legs after each retrograde arterial catheterisation. Absent or reduced arterial pulsations, substantially decreased blood pressure, pallor, and diminished skin temperature of the cannulated leg after the end of the procedure are reliable criteria for femoral artery obstruction.[2,4,5]

Persistence of impaired perfusion of the femoral artery indicates that treatment is needed. Surgical intervention, especially in younger children, is associated with a substantial risk of extending vascular damage.[2,5] In older children it has been undertaken with varying success.[1,4,5] The use of thrombolytic agents seems to be a preferable alternative.[4,5] These agents act directly or indirectly as plasminogen activators. They activate plasminogen, an inactive proteolytic enzyme in plasma, to produce the fibrinolytic enzyme plasmin.[10]

We treated our patients with streptokinase because this is the agent that has been most used in children for this indication. Streptokinase is a protein obtained from group C β haemolytic streptococci.[5,10] In our study femoral artery thrombosis occurred in nine patients after retrograde arterial catheterisation despite continued heparinisation. These patients were treated with systemic infusion of streptokinase. We did not perform local arterial infusion because this requires cannulation of another artery with the attendant risk of endothelial damage and possible formation of a new thrombus.[11]

In eight (89%) of nine patients systemic streptokinase treatment was successful. This accords with the results of two recently published studies.[4,5] The mean duration of treatment was greater in our patients than in these other studies (37·9 *v* 13·0 hours). Older thrombi are more resistant to fibrinolysis. Peripheral arterial thromboses that are > 24 hours old need longer treatment with streptokinase.[5,10] In our study the interval between the end of catheterisation and start of streptokinase treatment was not clearly related to how long treatment was needed. Despite laboratory signs of adequate fibrinolysis, streptokinase treatment was not immediately successful in one patient (11%) (the youngest in our series (9 days old)). Femoral artery perfusion was normal after 5 days, however. Recanalisation after spontaneous resolution of the thrombus is highly unlikely to have occurred in such a short period. Failure of thrombolytic treatment in neonates may be attributed to the lower concentrations of plasminogen or because the functional activity of plasminogen is less than the concentrations of plasminogen inhibitors (especially α_2 antiplasmin).[12–14] Sometimes the use of massive amounts of thrombolytic agents may be successful in these cases.[14] Activation of plasminogen by thrombolytic agents can result in haematological changes (particularly an increase of thrombin time and a decrease in plasma fibrinogen as well as an increase in plasma fibrin degradation products).[10,15] Monitoring of prothrombin time, partial thromboplastin time, thrombin time, plasma fibrinogen, and fibrin degradation products is a useful guide to adjusting thrombolytic treatment to avoid systemic bleeding complications.[5,10,15] In our patients there was no lengthening of prothrombin time and partial thromboplastin time, but the thrombin time increased and there was a moderate decrease in plasma fibrinogen concentrations—both signs of fibrinolysis (table 3).

Bleeding is the most hazardous complication of systemic thrombolytic treatment. We saw no serious bleeding complications in our study. Bleeding from the arterial entry site is the most common complication—particularly in patients undergoing balloon dilatation procedures. This complication was seen in one of our patients. Local compression will usually stop the bleeding.[4,5]

During thrombolytic treatment invasive procedures must be avoided.[10] Contraindications to thrombolytic treatment are the presence of or predisposition to intracranial haemorrhage, active internal bleeding (for example, gastrointestinal), recent major surgery (within 10 days), and a pre-existing bleeding tendency.[15] If serious bleeding develops thrombolysis must be stopped immediately and coagulation changes reversed by the use of fresh frozen plasma and cryoprecipitate.[10]

To avoid re-thrombosis after successful thrombolytic treatment or when thrombus formation persisted after treatment failure we treated our patients with heparin. The optimal anti-thrombotic regimen to prevent these problems still needs to be established. Heparin and/or aspirin have been recommended.[16] Like other investigators we did not encounter re-thrombosis in our patients.[4,5]

Treatment with streptokinase (a bacterial problem) is occasionally associated with an allergic reaction (rash, fever, nausea, a syndrome resembling serum sickness, and anaphylactic shock) especially in patients exposed to a recent streptococcal infection or streptokinase treatment.[10] Urokinase, a human product, is non-antigenic and can be used instead of streptokinase.[10] There were no allergic reactions in our patients.

The doses that we used and those used by others in children were not established by pharmacological investigations but were estimated from experience in adult patients. These doses were safe and effective but we do not know whether they are pharmacologically optimal.

In our study group the early use of streptokinase in the treatment of femoral artery thrombosis after percutaneous retrograde catheterisation in infants seemed to be beneficial. Because proof of the efficacy of treatment with streptokinase cannot be drawn from this study we recommend that a randomised, controlled study should be undertaken.

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Evaluation of pulmonary arterial pressure by Doppler colour flow mapping in patients with a ductus arteriosus

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Abstract

Blood flow in the pulmonary artery was studied by Doppler colour flow mapping and cardiac catheterisation in 19 patients with a ductus arteriosus and different pulmonary artery pressures. In the four patients with normal pulmonary artery pressures colour Doppler flow mapping showed multicoloured wide and long systolic and diastolic jets in the pulmonary artery. In the 15 patients with raised pulmonary arterial pressure the systolic jets varied from multicoloured to red and were thinner: in patients with considerably raised pulmonary arterial pressure the jets became redder during diastole. The Doppler velocity tracings showed that in patients with normal pulmonary artery pressures the mean peak systolic velocity was higher than the mean end diastolic velocity—so that in all four the ratio of peak systolic velocity to end diastolic velocity was <2. The mean peak systolic velocity was much higher than the mean end diastolic velocity in 13 of the 15 patients with raised pulmonary artery pressure; this meant that the ratio of peak systolic velocity to end diastolic velocity was >2 in 10 of 11 patients. The end diastolic velocity was significantly lower in those patients with raised pulmonary artery pressure than in those with normal artery pressure. There was an inverse linear correlation between the mean pulmonary artery pressure and end diastolic ductal jet velocity in 17 of the 19 patients.

Colour flow mapping and this quantitative Doppler technique can detect pulmonary artery hypertension in patients with a ductus arteriosus.

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The development of cross sectional echocardiography with pulsed and continuous wave Doppler techniques allows visualisation of the ductus arteriosus and recording of the flow velocity of ductal systolic and diastolic shunting in the pulmonary artery. A Doppler study showed that diastolic ductal flow was shortened in patients with pulmonary artery hypertension.[1] There were significant correlations between the haemodynamically determined instantaneous aorta to pulmonary arterial systolic pressure gradient and maximum instantaneous Doppler velocity across the ductus and between the instantaneous aorta to pulmonary artery diastolic pressure difference and minimum instantaneous Doppler velocity across the ductus.[2] The Doppler colour flow mapping technique not only images the ductus arteriosus but also characterises the systolic and diastolic jets in the pulmonary artery that are generated through the ductus.[3,4] The Doppler imaging technique showed distinct retrograde blood flow patterns caused by left to right shunting in the main pulmonary artery in patients with a ductus arteriosus[4] and a reduction in the diastolic ductal flow velocities when pulmonary arterial pressure was high.[3] The purpose of our study was to define various abnormal patterns of blood flow in the pulmonary artery caused by a ductus of various sizes and to determine the relation between pulmonary artery pressure and diastolic and systolic ductal blood flow velocities recorded in the pulmonary artery by Doppler colour flow mapping.

Patients and methods

We studied 19 patients (mean (SD) age 4·3 (1·9) years; mean (SD) weight 14·3 (3·1) kg). Seventeen had a ductus arteriosus and two also had coarctation of the aorta. Patients were examined in the supine position and infants were sedated with chloral hydrate. The heart was imaged from all sites with a Toshiba colour flow Doppler echocardiogram (Sonolayer-SSH-65 A). The ductus arteriosus was imaged from the left parasternal oblique plane and from high left parasternal positions.[5,6] We used a continuous wave Doppler beam with concomitant imaging of the pulmonary artery and descending aorta. We took special care to record both the systolic and diastolic flow velocities within the main pulmonary artery. We used colour Doppler flow mapping to image the high velocity jets in the pulmonary artery and by aligning the Doppler beam parallel with the jet we recorded maximum velocity spectra. Audio signals were used to record the velocities in the laminar portion of the jet.

Cardiac catheterisation was undertaken within one week of the echocardiographic study. A mixture of pethidine, chlorpromazine, and promethazine hydrochloride was used as a premedication. Blood gas saturation and two to three pressures were measured from the right heart chambers and descending aorta. In patients with coarctation of the aorta pressure was recorded in the ascending aorta. The ratio of pulmonary blood flow to systemic

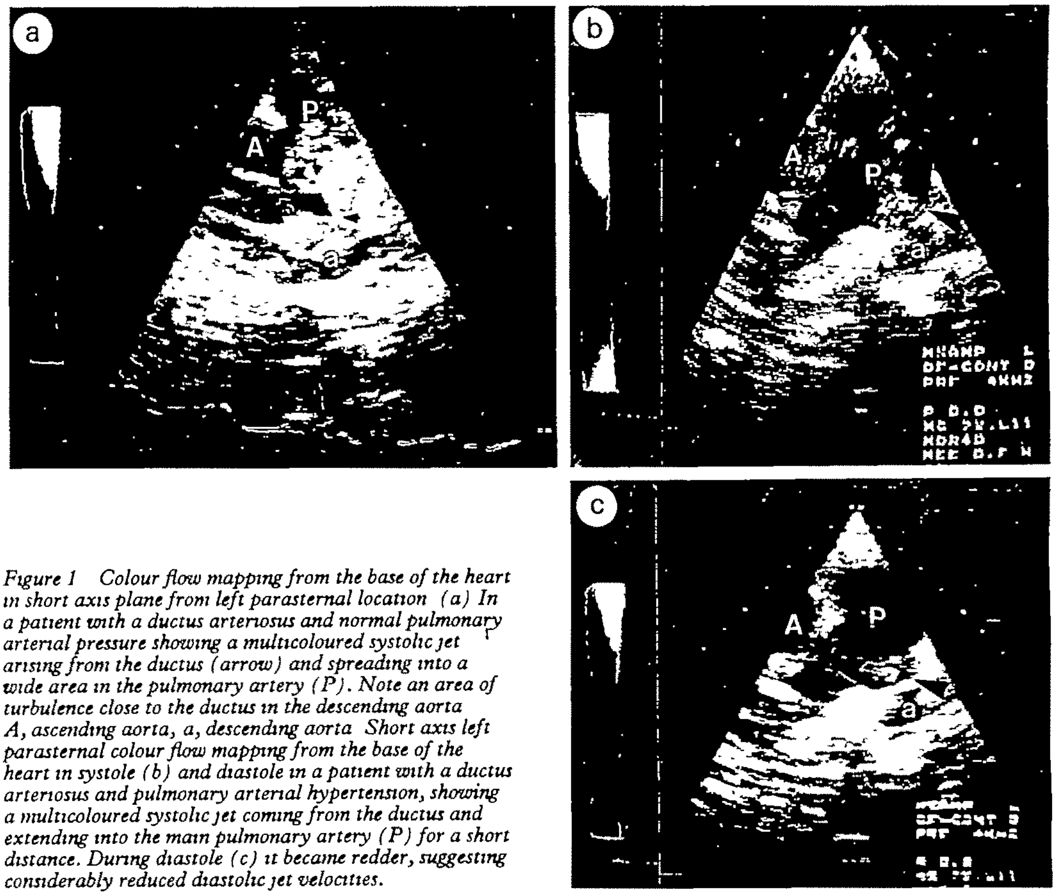

Figure 1 Colour flow mapping from the base of the heart in short axis plane from left parasternal location (a) In a patient with a ductus arteriosus and normal pulmonary arterial pressure showing a multicoloured systolic jet arising from the ductus (arrow) and spreading into a wide area in the pulmonary artery (P). Note an area of turbulence close to the ductus in the descending aorta A, ascending aorta, a, descending aorta Short axis left parasternal colour flow mapping from the base of the heart in systole (b) and diastole in a patient with a ductus arteriosus and pulmonary arterial hypertension, showing a multicoloured systolic jet coming from the ductus and extending into the main pulmonary artery (P) for a short distance. During diastole (c) it became redder, suggesting considerably reduced diastolic jet velocities.

blood flow (QP/QS) was calculated for 17 of 19 patients. The peak systolic velocity was measured manually from the timed velocity spectra that were recorded on a hard copy. The highest point on the systolic velocity spectrum was taken as the peak systolic velocity measurement. Three to four measurements were taken and the mean value was used for the correlations. The end diastolic velocity was measured at the peak of the R wave.

In one patient with considerably increased pulmonary artery pressure there was a drop out of diastolic velocities in the last part of diastole. In this patient we used the last portion of the diastolic spectrum to measure diastolic velocity. A mean of three to four measurements was taken. In four patients the systolic velocity spectrum was either not recorded or was incomplete. In two patients with significantly raised pulmonary arterial pressures, abnormal ductal flow velocities were not recorded in the pulmonary artery, in systole or diastole. These two patients showed no left to right shunt at cardiac catheterisation and one of them showed only a right to left shunt from the pulmonary artery into the descending aorta.

Results

QUALITATIVE STUDY

In patients with a ductus arteriosus the continuous wave record of the Doppler flow velocity profile of anterograde (normal) pulmonary blood flow (coded blue) was seen in the distal pulmonary arteries as a negative velocity spectrum (below the baseline) and concomitant systolic jet velocities caused by ductal left to right shunt as retrograde blood flow toward the pulmonary valve were recorded as positive velocity spectrum (above the baseline). Positive blood velocities continued to be recorded during diastole. This retrograde ductal systolic and diastolic jet flow could be mapped in the colour mode, and a multicoloured systolic jet could often be traced from the descending aorta, where a small area of multicoloured flow disturbance was seen, through the ductus along the lateral and superior wall of the main pulmonary artery in a retrograde direction. The distance to which systolic and diastolic jets extended into the pulmonary artery varied; with low pulmonary artery pressure the systolic jet extended in a retrograde direction right up to the pulmonary valve and eventually ended up in a vortex near the pulmonary valve where it reversed to flow in an anterograde direction. A multicoloured high velocity jet with wide lateral flow velocities extending a long way into the pulmonary artery was characteristic of a ductus arteriosus and low pressure in the pulmonary artery. The jet remained visible during both systole and diastole and the colour profile of the jet during systole and diastole did not vary a great deal in patients with normal pulmonary arterial pressure (fig 1a). Anterograde pulmonary flow (coded blue) was seen in the distal pulmonary arteries. Reversed flow during diastole (coded red)—that is towards the pulmonary valve—was seen near the bifurcation of the pulmonary arteries.[4] In those patients in whom pul-

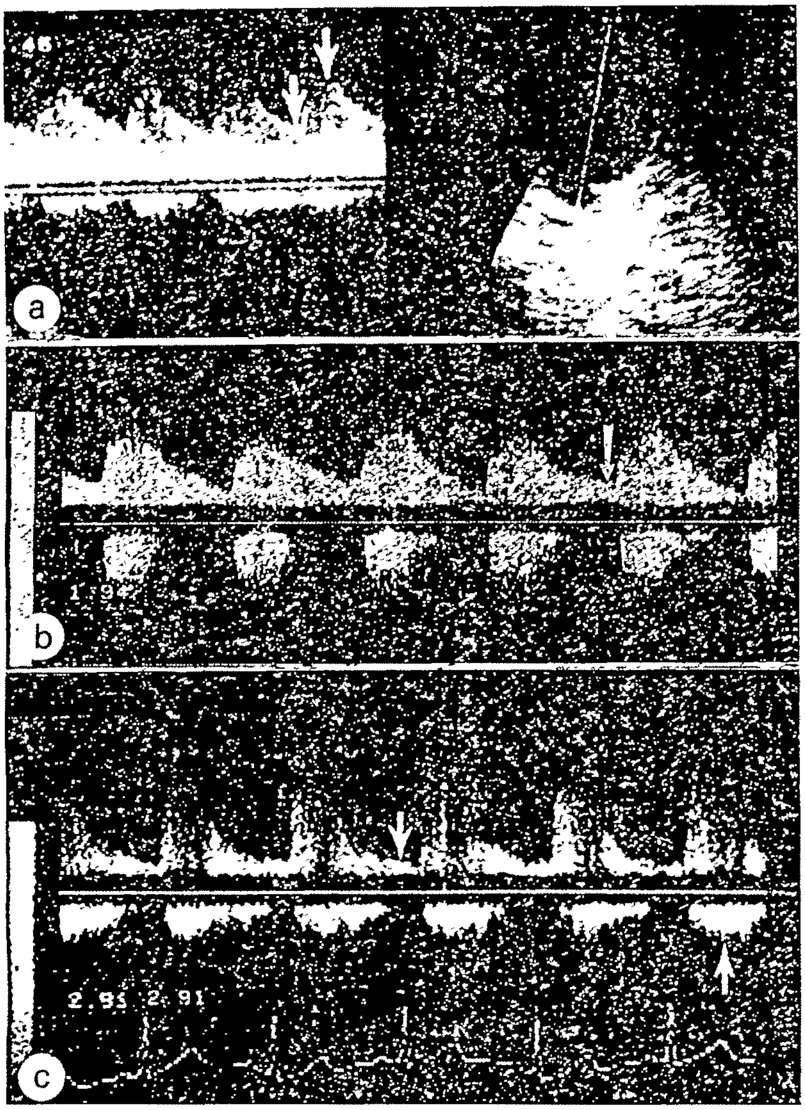

Figure 2 (a) Continuous wave Doppler velocity spectrum in the main pulmonary artery in a patient with a ductus arteriosus in whom the mean pulmonary artery pressure was 19 mm Hg Retrograde flow velocities were continuously above the baseline during systole and diastole because of left to right ductal shunting Both peak systolic (second arrow) and end diastolic velocities (first arrow) were relatively high. (b) Continuous wave Doppler velocity spectrum recorded in the pulmonary artery in a patient with mean pulmonary arterial pressure of 59 mm Hg Compared with peak systolic velocity the end diastolic velocity (arrow) was significantly reduced. Anterograde (normal) systolic pulmonary arterial flow velocities were recorded below the baseline (c) Velocity spectrum of a patient with a ductus arteriosus and mean pulmonary arterial pressure of 62 mm Hg The diastolic velocity was much reduced (arrow above the baseline). Arrow below the baseline shows anterograde (normal) flow velocities.

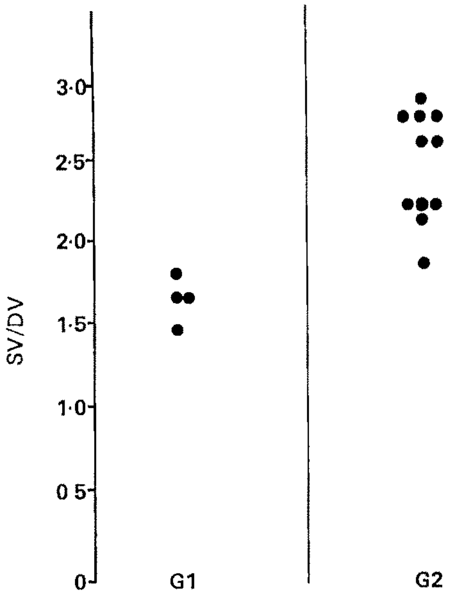

Figure 3 Peak systolic/end diastolic velocity ratio (SV/DV) in patients with low pulmonary artery pressures (G1) and high pulmonary artery pressures (G2) All but one of the 11 hypertensive patients had ratios > 2

monary arterial pressure was considerably increased and the left to right shunt was small—that is the QP/QS ratio was < 1·5—a small flame shaped red jet came from the ductus and extended a short distance into the main pulmonary artery during systole and diastole. In the patients with raised pulmonary arterial pressure, the colour coding of the systolic multicoloured jet was variable and depended upon the pulmonary arterial pressure (fig 1b). In patients with moderately raised pulmonary arterial pressure the multicoloured systolic jet was shorter and thinner and became more red during diastole because of a considerable reduction in the diastolic velocities (fig 1c). In one patient we did not see left to right ductal flow in the main pulmonary artery; however, the ductus image showed systolic and diastolic flow (coded blue) from the pulmonary artery into the descending aorta. Catheter studies (oximetry) in this patient did not show shunting and pressures in the pulmonary artery and aorta were similar. The only abnormal velocities recorded in this patient were from reversed flow from the pulmonary artery through the pulmonary valve into the right ventricle, which were due to pulmonary regurgitation caused by very high pulmonary arterial pressure.

QUANTITATIVE STUDY

Left to right ductal shunting was studied by recording abnormal positive flow velocities (above the baseline) during systole and dia-

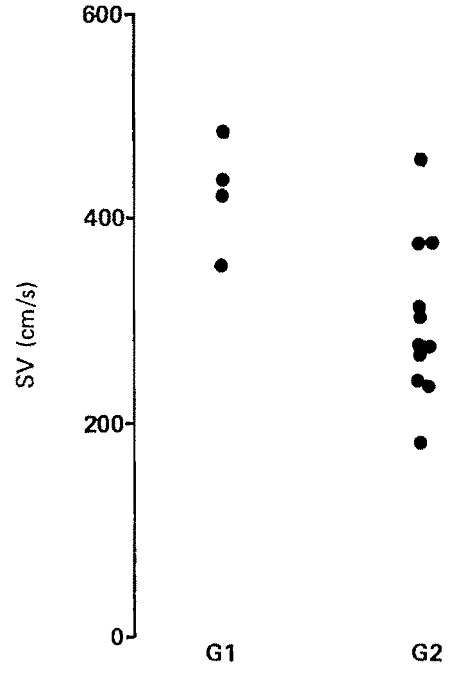

Figure 4 Peak systolic (SV cm/s) velocities in patients with low pulmonary artery pressures (G1) and high pulmonary artery pressures (G2) Peak systolic velocities were significantly lower in the hypertensive group (p < 0·01)

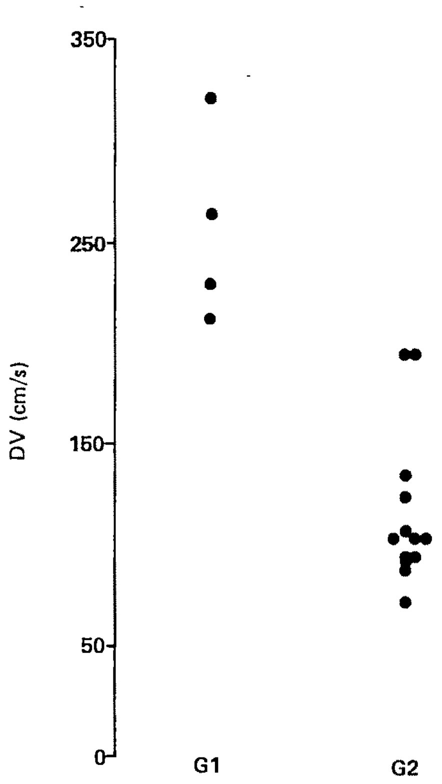

Figure 5 End diastolic velocities (DV cm/s) in patients with low pulmonary artery pressures (G1) and high pulmonary artery pressures (G2) There was no overlap of values in the normotensive and hypertensive groups ($p < 0{\cdot}001$).

stole (fig 2). Cardiac catheterisation showed that in four patients (group I) mean pulmonary arterial pressure was ⩽24 mm Hg (mean (SD) 20·3 (2·5) mm Hg) and the mean (SD) QP/QS ratio was 2·1 (0·48) (fig 2a). In 15 patients (group II) mean pulmonary artery pressure was >25 mm Hg (mean (SD) 55·1 (11·7) mm Hg). The mean QP/QS ratio in 13 of these 15 patients was 3·4 (1·7) (fig 2b and c). The mean peak systolic velocity in the four patients with lower mean pulmonary arterial pressure was 434 (52·9) cm/s and the mean end diastolic velocity was 264 (50·8) cm/s and the ratio of systolic velocity/end diastolic velocity was <2 (mean 1·68 (0·17). Mean peak systolic velocity (308 (78·3) cm/s) was measured in 11 of the 15 patients with higher pulmonary artery pressures (group II) and mean end diastolic velocity (118·6 (39·9) cm/s) was measured in 13. The ratio of peak systolic velocity to end diastolic velocity was >2 (mean 2·5 (0·37)) in the 10 patients and in one patient the ratio was 1·9 and the mean pulmonary arterial pressure was 37 mm Hg (fig 3). The peak systolic velocity was significantly lower in the patients with raised pulmonary artery pressures ($p < 0{\cdot}01$, fig 4); however, diastolic velocity was significantly reduced in this group (compared with the four patients with normal pulmonary artery pressures) ($p < 0{\cdot}001$), and this variable clearly separated the two groups (fig 5).

The end diastolic velocity correlated inversely with the mean pulmonary arterial pressure in all 17 patients in whom it was measured ($r = 0{\cdot}897$, $p < 0{\cdot}001$, SE 0·0387) (fig 6).

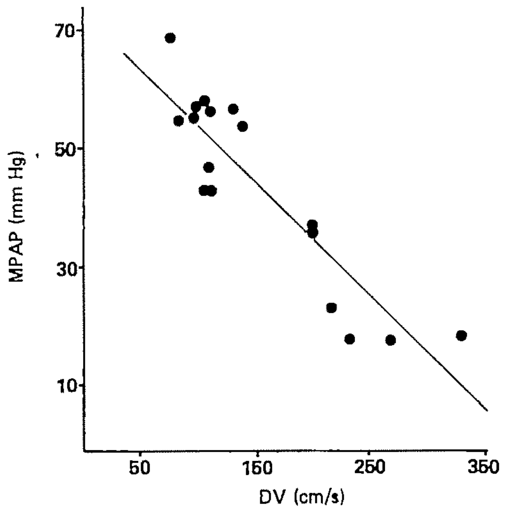

Figure 6 Mean pulmonary arterial pressure (MPAP) plotted against end diastolic velocity (DV cm/s) in 17 patients with a ductus arteriosus. An increase in mean pulmonary artery pressure was associated with proportionate reduction in diastolic velocity

Discussion

Our study confirms the previously reported colour Doppler profile of pulmonary systolic and diastolic blood flows in patients with a ductus arteriosus.[4] Retrograde continuous flow toward the pulmonary valve caused by left to right ductal shunting was seen during systole and diastole. This retrograde flow contained velocities that depended upon the size of the ductus and the pulmonary arterial pressure during systole and diastole. The distance to which a jet arising from the ductus extended retrogradely into the pulmonary artery was a function of pulmonary arterial pressure and the anterograde hydraulic force of forward systolic pulmonary blood flow on one hand and left to right ductal jet velocity on the other. In patients in whom pulmonary arterial pressure was normal, the anterograde hydraulic forces opposing the systolic retrograde flow in the ductal shunt were lower so that the systolic jet was wide with considerable lateral flow velocities and tracked along the lateral and superior walls of the main pulmonary artery up to the level of the pulmonary valve where a large vortex was seen with ductal flow joining the anterograde pulmonary blood flow. The areas around the systolic jet were blue (showing normal forward pulmonary arterial blood flow). The distance that the systolic and diastolic jets extended from the ductus to the pulmonary valve was reduced in proportion to the pulmonary arterial pressure. When pulmonary arterial pressure was significantly raised by increased pulmonary vascular resistance, anterograde hydraulic forces were increased and the systolic ductal jet was lean and thin and was considerably deflected toward the walls of the main pulmonary artery. During diastole the jet became more red, suggesting a considerable reduction in diastolic velocities. In patients with pulmonary arterial pressure that was near systemic values a red flame shaped jet was seen throughout systole and diastole. This extended a short distance from the ductus into the pulmonary artery. The diastolic jet velocities of these patients were much reduced (to <100 cm/s).

Thus our study showed that the colour coding of the systolic and diastolic ductal jets, their width, and the distance they extended into the pulmonary artery can be used to evaluate the pulmonary arterial pressure in patients with a ductus arteriosus.

Doppler measurement of the ductal shunting flows showed that systolic and diastolic velocities were significantly higher in patients with low pulmonary arterial pressure—so that the ratio of peak systolic velocity to end diastolic velocity was <2. Compared with peak systolic velocities the end diastolic velocities were considerably reduced in the hypertensive group so that the ratio of peak systolic to end diastolic velocity was >2 in most patients. So the ratio of peak systolic velocity to end diastolic velocity could be used to identify patients with pulmonary arterial hypertension. The only difficulty with this approach was that the peak systolic velocity could not be recorded in four patients. However, the absolute diastolic velocity measurement separated all patients with pulmonary artery hypertension from those without.

Our initial data showed a linear relation between the mean pulmonary arterial pressure and the end diastolic velocity measurement. We believe this relation would have been even closer if it had been feasible to record the Doppler velocity spectrum simultaneously with the measurement of pulmonary arterial pressure at cardiac catheterisation. Our study suggests that for clinical purposes mean pulmonary arterial pressure can be derived from the Doppler measurement of end diastolic velocity. The colour Doppler technique permits not only qualitative but also quantitative estimate of pulmonary arterial pressure in patients with a ductus arteriosus.

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Preoperative measurement of pulmonary vascular resistance in complete transposition of the great arteries

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Abstract

Transposition of the great arteries is frequently complicated by the early onset of pulmonary vascular disease. It is difficult to measure pulmonary blood flow by the Fick principle because the pulmonary arteriovenous oxygen content difference is small and bronchial blood flow is increased in this condition. In eight patients (mean age 7·7 years, range 3 months to 29 years) with transposition of the great arteries mass spectrometry was used to measure oxygen uptake and predict pulmonary end capillary blood oxygen content. The effects of the bronchial circulation were studied by computer modelling. There was close agreement between pulmonary end capillary and pulmonary vein blood oxygen contents but the resultant percentage difference in arteriovenous content difference was significant (mean (SE of difference)) (14·5(3·8)%). The effect of the bronchial circulation was to give spuriously high estimates of pulmonary blood flow. The error was greatest when oxygen consumption was low and aortic blood was very desaturated.

Rapidly progressive pulmonary vascular disease is an important complication of transposition of the great arteries.[1–3] It may occur as early as the first year of life,[4–6] whether or not the ventricular septum is intact[6–8] and despite the presence of pulmonary stenosis[5 9] or adequate banding of the pulmonary artery.[2 10] Assessment of severity is helpful in determining the nature and timing of operation. Measurement of pulmonary vascular resistance may not be reliable in these children because the high pulmonary artery saturation results in a low arteriovenous oxygen content difference.[9 10] Accurate determination of this difference is necessary for application of the Fick principle.[10–12] Furthermore, bronchial artery hypertrophy has been shown angiographically[9] and histologically,[1] and an increased bronchial blood flow may affect the measurements.[9] This paper reports our approach to the preoperative measurement of pulmonary blood flow in these children. We also discuss how reliable such measurements are likely to be. This assessment was based in part on computer modelling of the pulmonary and bronchial circulation.

Patients and methods

We report nine haemodynamic studies in eight patients. There were five male patients and three female patients, mean age 7·7 years, range three months to 29 years. All had transposition of the great arteries with communications between the circulations at atrial or ventricular level. Table 1 shows the full details. No patient had a ductus arteriosus at the time of the study. In all oxygen saturation was higher in the pulmonary artery than in the aorta. Patient 1 was studied on two occasions, three months apart, because of fears that pulmonary vascular disease had developed while he was awaiting operation. Flow was measured at diagnostic cardiac catheterisation while the patients were intubated and ventilated. Full details of the methods have been published elsewhere.[13–15]

In summary, fluid filled catheters were introduced percutaneously into the femoral artery and vein and positioned in the aorta and pulmonary artery respectively. For the measurements of pulmonary blood flow, oxygen consumption was measured by mass spectrometry (MGA 200), by the steady state, argon dilution principle.[13] Blood Po_2, pH, and base excess were measured on a Corning 165 blood gas analyser and used to calculate blood oxygen contents.[16] We assumed that the solubility of free oxygen in blood was 0 03 ml/mm Hg/l. End tidal Pco_2 was measured with the mass spectrometer and used to calculate the alveolar Po_2 from the alveolar air equation. This value was then used to calculate the oxygen content of pulmonary end capillary blood, which replaced the oxygen content of the pulmonary vein in the Fick equation. Whenever possible, we also sampled the pulmonary vein to check the validity of our assumption that the oxygen contents of the

Table 1 Additional diagnoses in patients with complete transposition of the great arteries

No	*Age (yr)*	*Sex*	*Diagnoses*
1	3/12	M	VSD/PS
2	7/12	M	ASD
3	8/12	M	ASD/VSD
4	21/12	F	VSD/PAB/Coarc/DA
5	26/12	F	VSD/PAB
6	10	M	PAB/TR
7	17	M	PAB/VSD
8	29	F	VSD

ASD, atrial septal defect, Coarc, coarctation; DA, ductus arteriosus (closed surgically before the study), PAB, pulmonary artery band, PS, pulmonary stenosis, TR, tricuspid regurgitation, VSD, ventricular septal defect

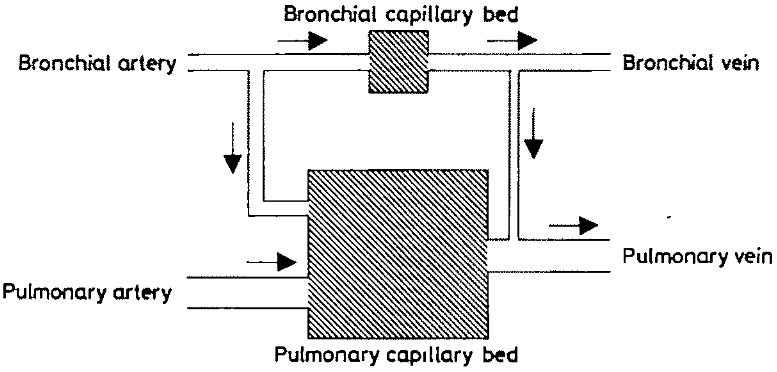


Figure 1 The blood supply to the lungs, as modelled in this paper. The bronchial arterial tree supplies both alveolar and bronchial capillaries; the bronchial capillaries drain into both bronchial and pulmonary veins.

pulmonary vein and pulmonary end capillary are similar.

COMPUTER MODEL

Bronchial artery blood flow cannot easily be measured in humans. The model (fig 1) therefore arbitrarily allocates values which increase from zero in steps of 100 ml/min per m^2. The oxygen content of bronchial artery blood equals that of aortic blood. Because it is desaturated, this stream of blood may be able to take up oxygen, particularly if it perfuses alveolar capillaries through precapillary anastomoses with the pulmonary circulation. This bronchial blood oxygen uptake would be indistinguishable from uptake of oxygen by blood in the pulmonary circulation. Therefore in the Fick equation used in the calculation of pulmonary artery blood flow, the numerator (pulmonary blood oxygen uptake) is overestimated. The effects of this can be modelled if the oxygen content of bronchial venous blood is known. In healthy individuals, approximately one third of the bronchial circulation drains into the right atrium via the bronchial veins, and two thirds drains into the left atrium via the pulmonary veins.[17] In neither route can bronchial venous oxygen content be measured, nor can it be assumed to be equal to that of vena caval blood. Bronchial venous blood cannot be more oxygenated than pulmonary end capillary blood whatever route it takes, so the two are assumed to be equal. If any bronchial venous blood is less saturated than pulmonary end capillary blood, then the uptake of oxygen by the bronchial circulation will be overestimated.

The steps in the calculation are as follows. An arbitrary value of bronchial blood flow (QBr) is allocated by the program. If the blood oxygen contents of pulmonary artery, aortic, and pulmonary end capillary blood are respectively $Cpao_2$, $Caoo_2$, $Cc'o_2$, then applying the Fick equation to the bronchial circulation,

$$QBr = Vo_2Br/(Cc'o_2–Caoo_2)$$

where Vo_2Br is the oxygen uptake in the bronchial circulation. After rearranging,

$$Vo_2Br = QBr \times (Cc'o_2–Caoo_2)$$

Total oxygen uptake (Vo_2T) = Vo_2Br + pulmonary capillary oxygen uptake. Application of the Fick equation to the pulmonary circulation gives

$$\text{Pulmonary capillary blood flow} = (Vo_2T–Vo_2Br)/(Cc'o_2–Cpao_2)$$

Therefore, pulmonary capillary blood flow can be calculated for as many different bronchial circulation blood flows as desired.

The model is written in FORTRAN 04 to run on the hospital mainframe computer (Prime 750). A full listing is available from AB. It could easily be adapted to run on a microcomputer.

Results

HAEMODYNAMIC DATA

Table 2, in which the patients are arranged in ascending order of age, shows total oxygen uptake, the calculated oxygen contents of blood in aorta, pulmonary artery, pulmonary vein, and pulmonary end capillary, and the values of pulmonary blood flow and pulmonary vascular resistance.

We compared the calculated oxygen content of pulmonary end capillary blood and the measured oxygen content of pulmonary vein blood. The mean difference between the two was 0·29 ml/dl (SD 0·43) measured in air (n = 5) and 0·27 (SD 0·20) measured in oxygen (n = 7). The difference was statistically significant (p = 0·0004) according to

Table 2 Detailed results of the studies of haemodynamic function in which calculations of pulmonary blood flow (Qp) and pulmonary vascular resistance (PVR) were based on pulmonary end capillary blood not pulmonary venous blood

			Blood oxygen content						
Patient no	*Insp*	*Vo_2*	*Ao*	*PA*	*PV*	*Pc′*	*PAP*	*Qp*	*PVR*
1a	100% O_2	160	24·34	23·00	24·34	24·79	35	9·0	3·3
1b	Air	173	16·03	19·07	20·58	21·04	38	9·0	3·7
	100% O_2	154	—	21·19	22·81	23·16	39	7·8	4·4
2	Air	234	11·11	22·15	24·73	24·72	15	9·1	1·0
	100% O_2	236	15·53	24·36	26·67	26·91	15	9·3	1·0
3	Air	88	15·48	18·40	21·23	21·14	23	3·2	6·4
	100% O_2	88	—	20·95	23·14	23·37	16	3·6	3·6
4	Air	162	18·64	20·38	—	24·23	15	4·2	1·8
	100% O_2	168	20·88	23·60	26·40	26·42	16	5·9	1·1
5	Air	190	17·07	19·10	26·00	26·96	33	2·4	11·9
	100% O_2	160	21·04	23·23	—	29·29	35	2·6	11·4
6	Air	166	16·94	17·31	—	18·81	51	12·3	3·0
	100% O_2	148	19·02	19·13	—	20·78	50	10·0	3·7
7	Air	154	24·31	27·47	—	29·31	17	8·3	1·5
	100% O_2	147	27·08	29·56	31·37	31·52	16	7·5	1·5
8	Air	240	25·45	28·96	30·81	30·93	84	9·4	8·5
	100% O_2	174	28·71	30·31	32·54	33·14	74	4·7	14·3

Oxygen consumption (Vo_2), ml/min per m^2, blood oxygen content, ml/dl; pulmonary artery pressure (PAP), mm Hg; pulmonary blood flow (Qp), l/min per m^2; pulmonary vascular resistance (PVR), mm Hg. l^{-1}.min.m^2.
Insp, inspired gas; Ao, aorta, PA, pulmonary artery; PV, pulmonary vein; Pc′, pulmonary end capillary.

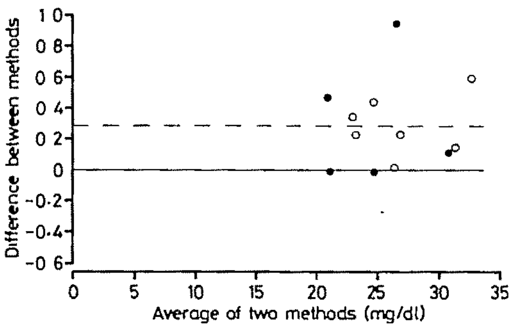


Figure 2 Comparison of oxygen contents of pulmonary venous and pulmonary end capillary blood. This plot shows that estimates of pulmonary end capillary blood oxygen content were systematically slightly greater than measured pulmonary venous blood oxygen content. Closed circles are measurements in air and open circles are measurements in 100% oxygen. The dotted line is the mean of all twelve points.

repeated measures analysis of variance, allowing for missing data.[18] Figure 2 shows the error and bias. If pulmonary end capillary blood was paired with pulmonary artery blood, the mean (SE) of the blood oxygen content differences across the pulmonary circulation was 2·78 (0·52) ml/dl; if pulmonary vein blood was used instead, the corresponding result was 2·47 (0·46) ml/dl. The mean percentage difference between these two sets of values was 14·5 (3·8) (range −3·2 to 33·9%). Figure 3 shows the error and bias.

Figure 4 shows the results of the bronchial circulation modelling. This shows the mean and 95% confidence intervals of the percentage error in pulmonary blood flow caused by unsuspected bronchial blood flow of 0·1–1·0 l/min per m^2. The results for a normal subject are shown for comparison. There is considerable individual variation; for a bronchial flow of 0·5 l/min per m^2, the error could have been as much as 32% or as little as 1·4%. The lower the total oxygen uptake, and the lower the aortic blood oxygen content, the greater the errors that were encountered.

FOLLOW UP DATA

We were able to compare measurements of pulmonary vascular resistance with lung structure in two patients. Patient 5 had Heath Edwards late grade III disease (her pulmonary vascular resistance was 10·5 units in air) and patient 6 had only grade I/II with a pulmonary vascular resistance on air of 3·7 units. Patient 1 had a Mustard's procedure, with closure of the ventricular septal defect and has done well postoperatively. Patients 2, 3, 4, and 7 are awaiting corrective operation. Patient 8 had a palliative Mustard's procedure, and a postoperative study showed a pulmonary vascular resistance of 9·9 units in air.

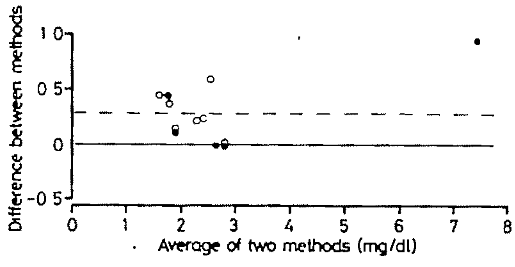


Figure 3 Comparison of differences in the pulmonary arteriovenous oxygen content when pulmonary end capillary blood and pulmonary venous blood are used. This plot shows that, because the arteriovenous oxygen content difference is so small, the minor discrepancies shown in figure 2 result in large discrepancies in the oxygen content differences Closed circles are measurements in air, open circles are measurements in 100% oxygen. The dotted line is the mean of all twelve points.

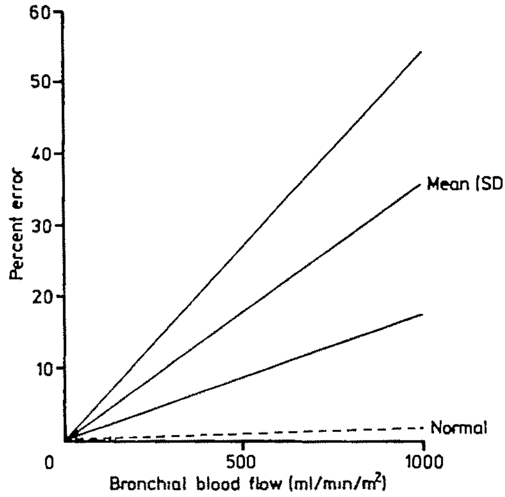


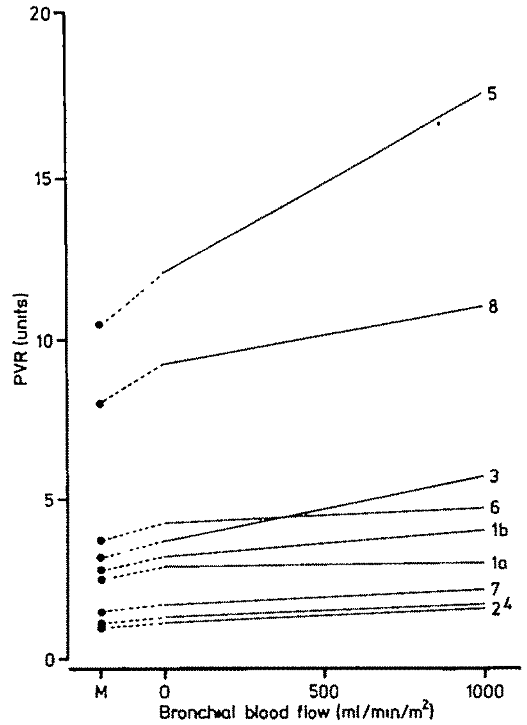
Figure 4 Results of the bronchial circulation model. The mean and 95% confidence intervals for the overestimate of pulmonary blood flow are plotted against bronchial blood flow. The dotted line shows equivalent results for a control

Discussion

The conventional solution of the Fick equation for organ blood flow assumes that either the concentration difference or the flow rate or both are constant while the measurement is made.[9] This is rarely if ever true. The smaller the arteriovenous concentration difference, the greater the error that these assumptions produce.[9] This paper highlights two particular problems in the measurement of pulmonary vascular resistance in transposition of the great arteries, namely the difficulty of ascertaining the true pulmonary vein blood oxygen content and the possible role of the bronchial circulation.

The lungs are drained by four pulmonary veins. Even in the supine position during cardiac catheterisation there are likely to be regional variations in pulmonary gas exchange. This could result in variations in the oxygenation of blood in the four pulmonary veins, of which one only is routinely sampled. Blood flow is pulsatile at all levels of the pulmonary circulation,[19] and hence red cell capillary transit times will vary with the phase of the cardiac and respiratory cycles. This will result in small phasic alterations in blood oxygen content with time. Slow withdrawal of a systemic blood sample would partially overcome these effects if there were no intracardiac shunts. But this procedure is open to the criticism that it produces a time average sample at a point not a volume average at the area of sampling.[9] In transposition the choices are either to use a sample from a single pulmonary vein or to use the alveolar air equation to predict pulmonary end capillary oxygen content. This latter approach assumes a uniform distribution of ventilation to perfusion ratios within the lung, but, particularly if the patient is ventilated on 100% oxygen, even large inequalities will not significantly affect the calculated oxygen content. This equation thus provides a way of partially overcoming regional differences but takes no account of the anatomical intrapulmonary shunt. There is good agreement between the end capillary and pulmonary vein blood, as found in other patients with congenital heart disease.[15] However, even a minor systematic difference between the two, results in big differences in calculated flow if the

Figure 5 Lowest pulmonary vascular resistance (PVR, mm Hg l^{-1}.min m^2) plotted against bronchial blood flow QBr, ml/min/m^2. M is the actual measurement made in pulmonary end capillary blood. The difficulties of getting a true pulmonary vein sample were estimated as likely to underestimate true PVR by 15% (see text; plotted as QBr = 0·0). The remaining points are based on the additional effects of the bronchial circulation, which were modelled as described.



arteriovenous blood oxygen content difference is small.

The nature of bronchial blood flow in this condition may also lead to inaccuracy. Normally, bronchial artery blood is nearly fully saturated and can take up far less oxygen than pulmonary artery blood. In transposition this is not the case. Normal bronchial blood flow has been estimated as 50–100 ml/min per m².[20] Our computer model has shown that even modest increases in bronchial blood flow can result in significant overestimation of pulmonary blood flow.

Other workers have confirmed that the Fick method overestimates pulmonary blood flow.[11 12] Dye dilution or thermodilution with pulmonary artery sampling will not be affected by bronchial blood flow,[11] but such measurements are difficult to interpret in infants with intracardiac shunting. Pulmonary blood flow has been measured from angiograms[12 21 22] but only in infants with no ventricular septal defect. The dose of contrast necessary precludes repeated measurements to assess any response to vasodilators. It is therefore likely that the Fick method will continue to be used and we believe it provides useful information if correctly interpreted. The follow up data, although incomplete, nevertheless support the view that resistance measurements may be valuable. High values were found with severe pulmonary vascular disease (patient 5) or a high resistance after palliative operation (patient 8), when the more normal pattern of oxygen saturations allows greater certainty about the measurements. Low values were found with only mild pulmonary vascular disease (patient 6) or a good outcome after operation (patient 1).

These data suggest that the measured lowest pulmonary vascular resistance is the "best case". The "worst case" is found by modelling the effects of the bronchial blood circulation and adding 15% for the effects of the problems of pulmonary venous sampling. Figure 5 shows this approach in our patients. Pulmonary vascular resistance is plotted against bronchial blood flow, to show the "best" and "worst" cases. In many patients the decision to operate can be reached without recourse to these calculations. In patients where there is doubt, we believe that such calculations may be helpful, permitting the importance (or otherwise) of the uncertainties in the conventional calculations to be modelled. In our laboratory, a lowest resistance of 6·5 units was associated with inoperable pulmonary vascular disease.[23] So if the "best case" is significantly greater than 6·5 units, then only palliative procedures should be offered; if the "worst case" is less than 6·5 units, then corrective operation can be considered. If the possible range of resistance spans 6·5 units, then a lung biopsy is needed to assess the disease.

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Br Heart J 1990;63:304–7

Early diastolic clicks after the Fontan procedure for double inlet left ventricle: anatomical and physiological correlates

Andrew N Redington, Kit-Yee Chan, Julene S Carvalho, Elliot A Shinebourne

Abstract

M mode echocardiograms and simultaneous phonocardiograms were recorded in four patients with early diastolic clicks on auscultation. All had double inlet left ventricle and had undergone the Fontan procedure with closure of the right atrioventricular valve orifice by an artifical patch. The phonocardiogram confirmed a high frequency sound occurring 60–90 ms after aortic valve closure and coinciding with the time of maximal excursion of the atrioventricular valve patch towards the ventricular mass. One patient had coexisting congenital complete heart block. The M mode echocardiogram showed "reversed" motion of the patch towards the right atrium during atrial contraction. Doppler flow studies showed that coincident with this motion there was forward flow in the pulmonary artery with augmentation when atrial contraction coincided with ventricular systole.

The early diastolic click in these patients was explained by abrupt cessation of the motion of the atrioventricular valve patch towards the ventricular mass in early diastole. In one patient atrial contraction led to a reversal of this motion and was associated with forward flow in the pulmonary artery.

For many patients with complex congenital heart disease the only surgical option for long term palliation is the Fontan operation[1] or one of its modifications.[2] While most survivors are clinically well after these procedures, abnormal physical signs such as cyanosis, arrhythmia, fluid retention, and heart murmurs are common. Indeed, in a recent review they were found in 62% of patients.[3] We report four patients in whom the previously unreported auscultatory sign of an early diastolic click was heard. Simultaneous M mode echocardiography and phonocardiography showed the origin of this sound.

Patients and methods

Four patients (aged 4–18 years) with loud early diastolic clicking sounds noted on routine auscultation underwent detailed investigation by echophonocardiography. All patients had situs solitus with the usual atrial arrangement. The atrioventricular connection was univentricular, all patients having double inlet ventricle with two atrioventricular valves. All had previously undergone a Fontan type procedure with direct atriopulmonary anastomosis. In two patients a valved homograft was interposed between the right atrium and pulmonary artery. Each patient had the right atrioventricular valve closed by either a single or double layer of Dacron cloth sewn into the floor of the right atrium. The main pulmonary artery was tied off in all.

Cross sectional, M mode, and pulsed wave Doppler echocardiograms with simultaneous electrocardiogram and phonocardiogram were recorded on a Hewlett-Packard 77020A ultrasound system. The phonocardiogram was recorded over the point on the chest where the diastolic click was best heart on auscultation, usually in the fourth left intercostal space close to the sternum. M mode echocardiograms from the left atrioventricular valve, the aortic valve, and the patch over the right atrioventricular valve were recorded with the simultaneous electrocardiogram and phonocardiogram. In one patient, who had congenital complete heart block, an M mode recording was made of the transverse diameter of the right atrium viewed from a subcostal position. Pulsed wave Doppler flow measurements in the superior and inferior venae cavae (caval veins) and the proximal left pulmonary artery were also recorded in this patient. All recordings were made with a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 100 mm/s.

Results

The phonocardiogram confirmed the presence of an early diastolic click in each patient. This was recorded as a high frequency sound occurring 60–90 ms after the initial high frequency oscillations associated with aortic valve closure, the timing of which was confirmed from the M mode echocardiogram of the aortic valve. There was an inconsistent relation between the sound and left atrioventricular valve motion (fig 1). In each patient, however, the onset of the sound coincided with the time at which the right atrioventricular valve patch had reached its maximal excursion in early ventricular diastole (fig 2).

The patient with congenital complete heart block was studied in further detail. Figure 3 shows a recording of the motion of the right atrioventricular valve patch and its relation to the P wave of the electrocardiogram and subsequent atrial contraction. It is clear from this

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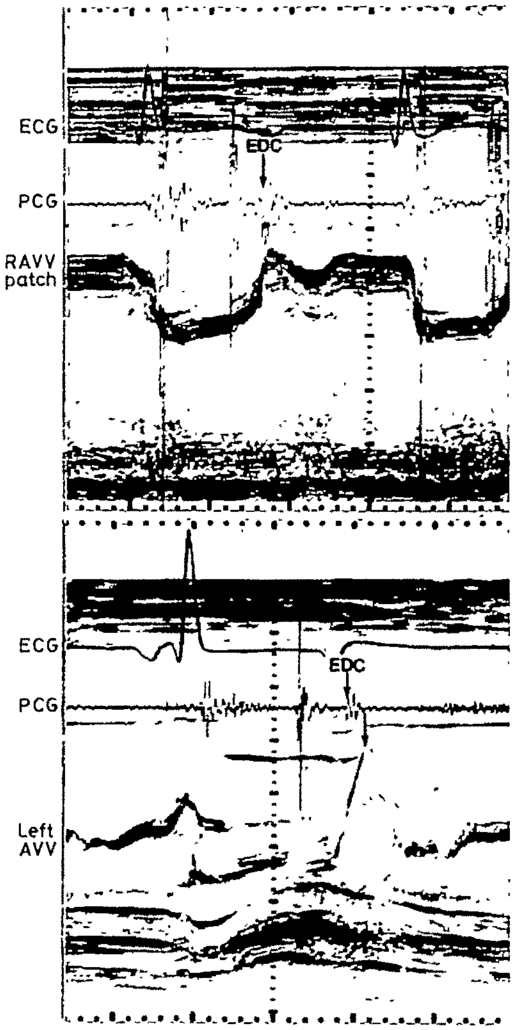

Figure 1 M mode recordings taken from the right atrioventricular valve (RAVV) patch (top panel) and the left atrioventricular valve (left AVV, bottom panel) in the same patient. The early diastolic click (EDC) coincides with the abrupt cessation of movement of the patch towards the ventricle in early diastole and is not related to the motion of the left atrioventricular valve. ECG, electrocardiogram; PCG, phonocardiogram.

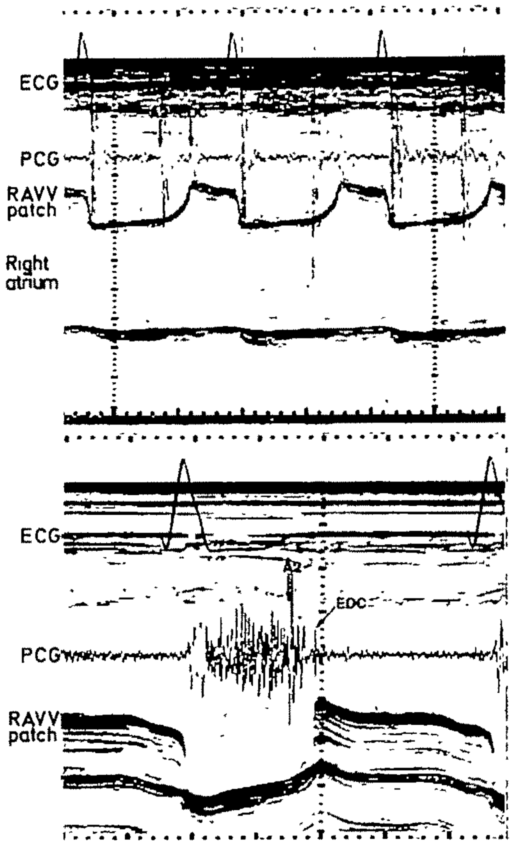

Figure 2 M mode recordings of the right atrioventricular valve (RAVV) patch in two patients In both the early diastolic click (EDC) occurred approximately 80 ms after closure of the aortic valve. ECG, electrocardiogram, PCG, phonocardiogram.

recording that atrial contraction was associated with movement of the patch away from the ventricular mass and towards the right atrium. When this occurred in early diastole there was a prolongation of the interval between aortic valve closure and the early diastolic click (fig 3(A)). This motion presumably reflects a pressure change between ventricle and atrium. Some light was shed on the nature of this pressure change when the atrial dimension and pulsed wave Doppler flow recordings were examined. Figure 4 shows that during atrial systole there was flow away from the atrium, with "reversed" flow in the venae cavae (caval veins) and forward flow in the proximal left pulmonary artery after the P wave of the electrocardiogram. Interestingly, this flow was augmented when the P wave coincided with or was close in timing to the QRS complex. The M mode recording from the right atrium showed that the transverse diameter decreased with atrial systole with the atrial septum moving towards the right atrium after the P wave (fig 4).

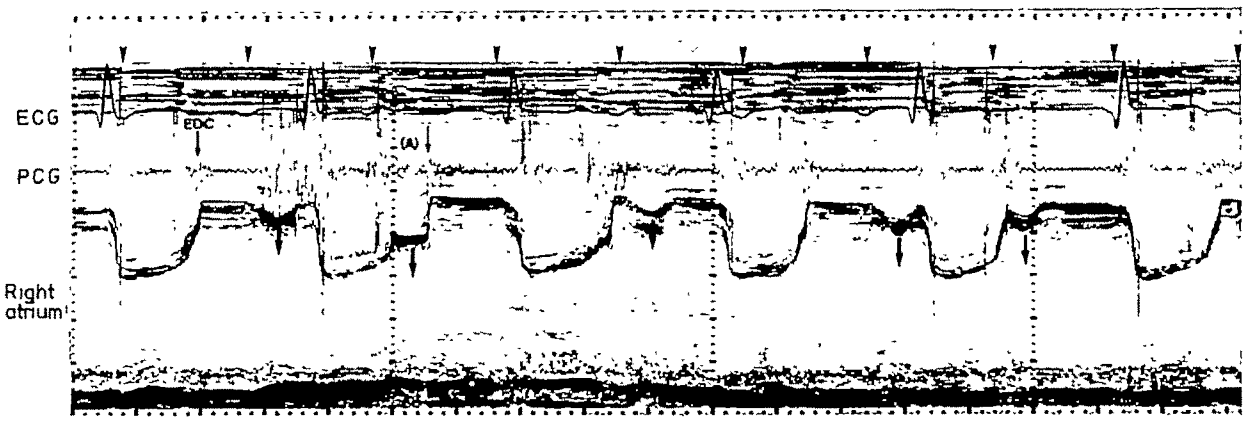

Figure 3 M mode recording of the right atrioventricular valve patch in the patient with congenital complete heart block. The P wave of the electrocardiogram (ECG) is marked along the top. When the P wave occurred in diastole the patch moved away from the ventricle towards the right atrium (marked with arrows) The early diastolic click (EDC) was delayed when atrial contraction occurred towards the end of systole (A). ECG, electrocardiogram; PCG, phonocardiogram.

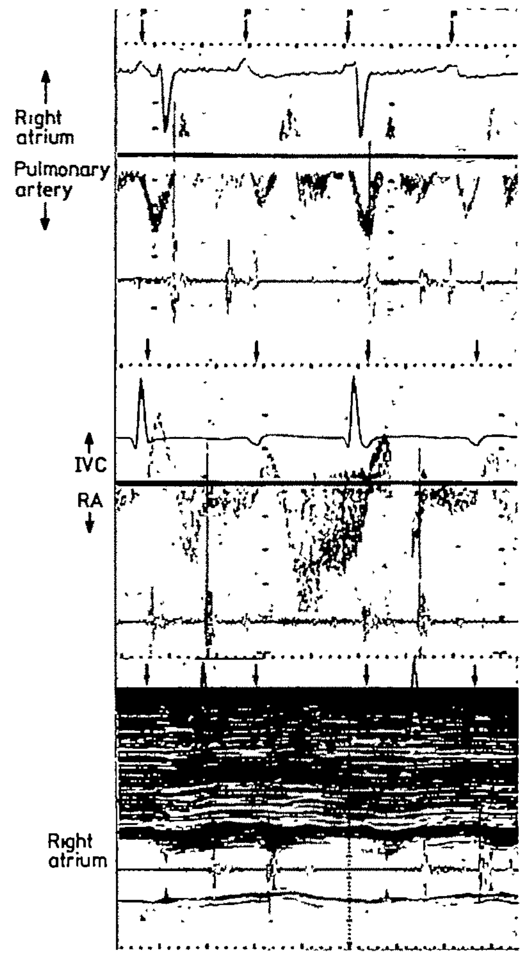

Figure 4 Pulsed wave Doppler recordings in the proximal left pulmonary artery (top panel) and inferior vena cava (IVC, middle panel) from the patient with complete heart block. The bottom panel shows the M mode recording of the transverse diameter of the right atrium. (The P wave of the electrocardiogram is marked by an arrow at the top of each recording—see text for details.)

Discussion

We showed that the early diastolic click heard in patients with double inlet left ventricle after the Fontan procedure coincides with the maximal early diastolic excursion of the synthetic material used to close the right atrioventricular valve orifice. As such, its origins are similar to those of the opening snap heard in patients with mitral or tricuspid stenosis.[4-6] High frequency opening sounds are frequently heard in patients with Ebstein's anomaly of the tricuspid valve. It was in these patients that M mode recordings with simultaneous phonocardiography were first used to show their origin.[7] In all these groups of patients the sound has been shown to coincide with the abrupt cessation of forward motion of the valve cusps at the beginning of early rapid ventricular filling. The similar timing of the early diastolic click in our patients, 50–80 ms after aortic valve closure, supports the idea that the sound is generated by the rapid deceleration of the valve cusps, and is further evidence against the suggestion that the snap heard in mitral stenosis is related to an abrupt closing motion of a previously opened mitral valve,[8] because the patch of material in our patients was imperforate with no potential for cusp closure.

Examination of the motion of the right atrioventricular valve patch in our patient with congenital complete heart block gives us the opportunity to examine the role of atrial contraction in the circulation after the Fontan procedure. As might be expected there was a variable relation between atrial and ventricular contraction in this patient. Figure 3 shows that other than during ventricular systole, the P wave of the electrocardiogram was followed by motion of the patch away from the ventricular mass and towards the right atrium. This is the opposite to what might be expected and presumably reflects a pressure transient between the left ventricle and right atrium. It is clear from fig 4 that the right atrium is emptying at this time; the transverse dimension decreases and there is flow away from the right atrium in the venae cavae (caval veins) and pulmonary artery. Furthermore this flow is augmented when atrial and ventricular systole are synchronous (when the atrioventricular valve patch is already maximally displaced towards the right atrium). It is clear, therefore, that right atrial contraction is contributing to forward flow in the pulmonary artery. This is consistent with previous studies that have shown the effect of atrial contraction[9 10] although its haemodynamic importance has been doubted.[11] It is difficult to explain the motion of the atrioventricular valve patch away from the left ventricle during atrial systole under these circumstances, however. The M mode recordings of the left atrioventricular valve confirmed that it opens shortly after the P wave on the electrocardiogram. It is possible that active contraction of the left atrium leads to an abrupt rise in left ventricular pressure so that right atrial pressure is exceeded, so pushing the patch towards the right atrium. An alternative explanation for this unexpected motion is that it results from an active process rather than a purely passive one. Previous studies have shown that the atrioventricular valve ring follows a similar pattern of motion,[12 13] that is, with atrial systole it moves towards the atrium, away from the ventricular mass. This is explained by the pattern of insertion of atrial myocardium at right angles to the ring. Thus this motion may be explained if the patch, which is stitched on to or just above the atrioventricular valve ring, moves with this structure during atrial systole.

Irrespective of the mechanism, it seems likely that loss of right atrial contraction in this patient would lead to a fall in cardiac output. It is certainly the case that loss of sinus rhythm in patients after the Fontan procedure is often associated with clinical deterioration, although this is clearly multifactorial. It is perhaps more controversial to suggest that synchronous atrial and ventricular pacing may be a possible approach to improving cardiac output in these patients, particularly when there is a normal heart rate and thus less dependence on the atrial contribution to ventricular filling. This is entirely speculative, however, and cannot be recommended without detailed haemodynamic monitoring.

The early diastolic click that occurs after the Fontan procedure for double inlet left ventricle is related to the abrupt cessation of motion of the right atrioventricular valve patch towards the ventricle. In some patients right atrial contraction may make an important contribution to forward flow in the pulmonary artery, which may be augmented when it coincides with ventricular systole.

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VIEWS FROM THE PAST *Myron C Prinzmetal*

Prinzmetal came to London to work with Lewis before the second world war and continued his studies on arrhythmias even though this was no longer the main thrust of Lewis's work; but Lewis's influence persisted after Prinzmetal had returned to the United States to the Cedars of Lebanon Hospital in Los Angeles. During the war he and Lewis's chief technician, John Honour, exchanged material on the Wolff-Parkinson-White syndrome. While Prinzmetal's book on *Auricular arrhythmias* (written with several collaborators) is now mainly of historical interest, he is still remembered eponymously for his description of variant angina. His career was ended soon after this discovery by the onset of a debilitating illness which kept him housebound until his death three years ago (Lewis collection).

DENNIS M KRIKLER

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CASE REPORTS

Sudden death in hypertrophic cardiomyopathy with normal left ventricular mass

Barry J Maron, Amy H Kragel, William C Roberts

Abstract

An active, healthy, and symptom free 16 year old boy with a family history of hypertrophic cardiomyopathy died suddenly while walking home from school. Necropsy showed absence of left ventricular hypertrophy (that is, normal heart weight), though the characteristic histological abnormalities of hypertrophic cardiomyopathy, such as cardiac muscle cell disorganisation and abnormal intramural coronary arteries, were present. It is likely that this patient had hypertrophic cardiomyopathy and died before left ventricular hypertrophy developed.

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Hypertrophic cardiomyopathy is a primary myocardial disease, often inherited, in which the morphological and clinical features are diverse.[1-4] The most characteristic anatomical feature of the disease is left ventricular hypertrophy in the absence of ventricular dilatation, unassociated with another cardiac or systemic disease which itself could produce left ventricular hypertrophy.[5]

In patients with hypertrophic cardiomyopathy, however, left ventricular hypertrophy is not always fully expressed within the first two decades of life.[6] In children with this disease left ventricular hypertrophy is often progressive or develops for the first time when body growth and maturation accelerate.[1,6]

Sudden death and cardiac arrest are the most devastating consequences of hypertrophic cardiomyopathy and they are most common in youthful patients with few or no symptoms[2,7,8] and substantial left ventricular hypertrophy.[1,2,8,9] The boy with hypertrophic cardiomyopathy that we describe died suddenly before the typical gross morphological features of the disease developed.

Case report

A 16 year old boy complained of feeling unwell at the end of the school day. Shortly afterwards he collapsed while walking home. Onlookers promptly started cardiopulmonary resuscitation, but these measures were unsuccessful.

According to his mother, the boy had been active, healthy, and in generally good physical condition until the day he died. He had not been involved in competitive athletics, but had often participated in bowling and occasionally lifted weights. He used neither drugs nor alcohol. There was, however, a strong family history of cardiac disease[1] (fig 1). His mother, brother, maternal aunt, and two maternal uncles have clinically and echocardiographically confirmed hypertrophic cardiomyopathy. These relatives showed various patterns of asymmetrical left ventricular hypertrophy.[1-4] The maximum ventricular septal thickness in the relatives ranged from 17 mm to 28 mm; none had systolic anterior motion of the mitral valve. The patient's maternal grandmother died at age 42 with congestive heart failure of uncertain cause (heart weight at necropsy was 530 g).

A complete necropsy was performed. The patient was 1·70 m tall and weighed 66 kg. He

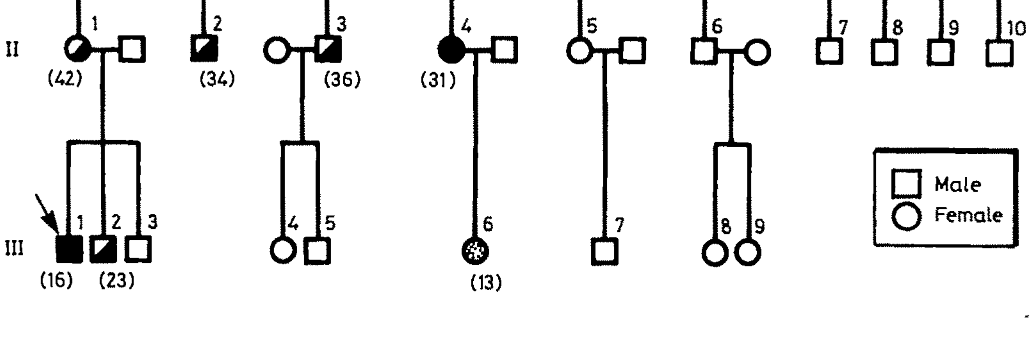

Figure 1 Pedigree of the patient (arrow) described in this report. Solid symbols indicate death from hypertrophic cardiomyopathy; those represented by half filled symbols are alive but affected by hypertrophic cardiomyopathy Open symbols indicate that no clinical data are available The stippled symbol represents a patient with symptoms suggestive of hypertrophic myopathy who was never investigated clinically. Ages are given in parentheses.

was well developed and well nourished. Mass spectrophotometric analysis for over 300 drugs (including volatile alcohols, narcotics, antihistamines, phenothiazines, barbiturates, synthetic narcotics, various sedatives, and cocaine) were performed on blood, urine, and lung tissue, and all were negative. All non-cardiac organs were normal.

The heart weighed 330 g and was judged to be within normal limits for sex and body size (that is ≤345 g according to Ludwig,[10] <380 g by the standards of Reiner,[11] and <420 g according to Kitzman *et al*[12]). In addition, the absolute heart weight (and heart weight corrected for body weight) of the patient was the lowest among the 75 weighed specimens from male patients ≥15 years old with hypertrophic cardiomyopathy who died of cardiac or non-cardiac causes and were studied in the Pathology Branch from 1960 to 1988 (fig 2D).

The epicardium was smooth and glistening and subepicardial adipose tissue was not increased. The ventricular and atrial chambers were non-dilated and the cardiac valves were normal (fig 2A). The thickness of the ventricular septum and left ventricular free wall did not exceed 15 mm (normal thickness ≤15 mm) in nearly all segments of the left ventricular wall (fig 2A). Limited portions of the distal (caudal) left ventricular free wall were up to 17 or 18 mm in thickness. Thickening of these small regions of wall were believed to be postmortem changes[13] rather than segmental hypertrophy,[14] in view of the patient's overall normal heart weight. There was no grossly visible myocardial necrosis or fibrosis nor any mural endocardial plaques. The epicardial coronary arteries were widely patent without evidence of atherosclerotic plaques.

The sinoatrial and atrioventricular nodal areas were dissected, serially sectioned, and examined every 8 μm; no abnormalities of the conducting tissue or small arteries were identified. In addition, seven transverse blocks of left ventricular myocardium were obtained, including four from the proximal (cephalad), middle, and distal (caudal) regions of the ventricular septum and three from the left ventricular free wall at the same levels. Histological sections (6 μm thick) were stained with haematoxylin and eosin and by the Movat method and examined by light microscopy.

Numerous foci of disorganised cardiac muscle cells were identified in which adjacent cells or bundles of cells were arranged at oblique and perpendicular angles to one another (fig 2B).

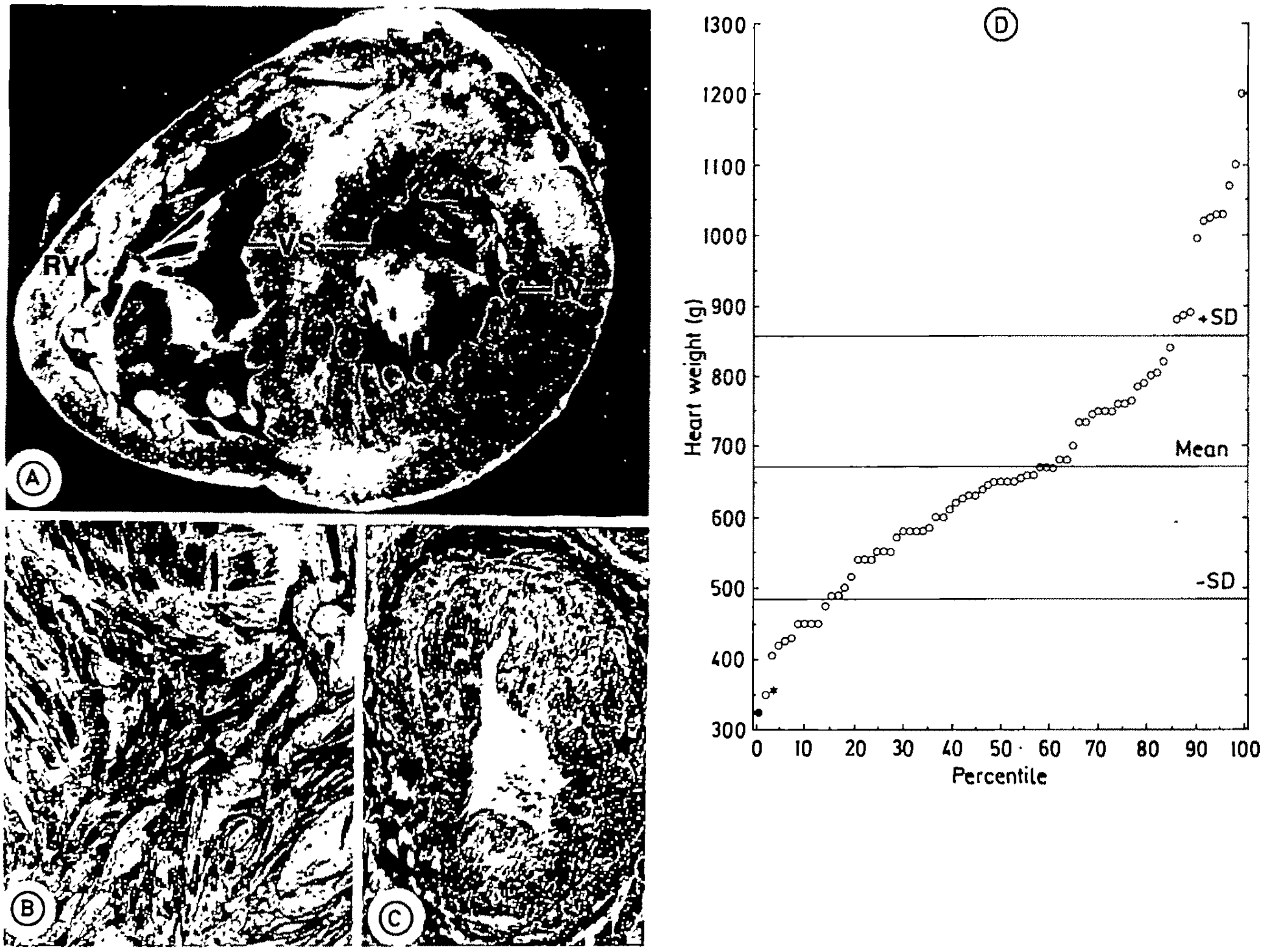

Figure 2 (A) Transverse section of the basal portion of the heart (which was of normal overall weight) showing non-dilated left ventricular cavity and normal ventricular septal (VS) and left ventricular free wall (LV) thicknesses; RV, right ventricular wall. (B) Region of cardiac muscle cell disorganisation in the left ventricular free wall, in which adjacent cells were oriented obliquely and perpendicularly. Haematoxylin and eosin stain, original magnification × 80. (C) Abnormal intramural coronary artery showing thickened wall and apparently narrowed lumen. Movat method; original magnification × 80. (D) Heart weights of 75 male patients with hypertrophic cardiomyopathy in the Pathology Branch registry. The solid symbol represents the patient reported here; the asterisk identifies the patient with the next lowest heart weight, a 49 year old man without a history of cardiac symptoms who died of renal cell carcinoma

We measured the overall extent of cellular disorganisation from photographic enlargements of the histological sections.[14] Of the cardiac muscle cells analysed, 17% in the left ventricular free wall and 4% in the ventricular septum were judged to be disorganised. In addition, we identified eight abnormal intramural coronary arteries with thickened walls and apparently narrowed lumen[15] (five in the septum and three in the free wall) (fig 2C).

Discussion

All earlier studies of patients with hypertrophic cardiomyopathy who died suddenly (or survived a cardiac arrest) reported left ventricular hypertrophy and usually a considerable increase in left ventricular mass.[1 2 9 16] Our patient, however, did not show the gross morphological features that are typical of hypertrophic cardiomyopathy. The heart weight was within normal limits,[10–12] and there was no mitral valve thickening, mural endocardial plaque in the left ventricular outflow tract, or left atrial enlargement. Therefore, the anatomical diagnosis of hypertrophic cardiomyopathy in our patient depended on the histological findings. For example, disorganisation of cardiac muscle cells in the left ventricular myocardium was more extensive than that found in diseases other than hypertrophic cardiomyopathy or in normal controls.[14] Using a previously described morphometric mapping technique,[14] we calculated that cellular disorganisation constituted almost 20% of left ventricular free wall myocardium (while the ventricular septum was less severely affected). In addition, we identified several abnormal intramural coronary arteries with thickened walls and apparently narrowed lumens, typical of those commonly seen in hypertrophic cardiomyopathy.[15] These histological findings and the family predisposition to hypertrophic cardiomyopathy (five had the disease) strongly suggest that he died of hypertrophic cardiomyopathy before left ventricular hypertrophy developed.

At present, members of families with hypertrophic cardiomyopathy are advised that those relatives who seem to be unaffected by the disease (that is, do not show left ventricular hypertrophy on echocardiography) are not at that time at risk of sudden death or the development of symptoms. It is possible that the identification of other patients who die suddenly in the absence of hypertrophy will alter our perceptions about the course of hypertrophic cardiomyopathy and our approach to the genetic counselling of affected families. None the less cases of sudden death from hypertrophic cardiomyopathy before left ventricular hypertrophy appears are likely to be uncommon.

We cannot be certain that left ventricular hypertrophy and wall thickening would not have developed in our patient. Indeed, previous echocardiographic studies have shown that children with a genetic predisposition to hypertrophic cardiomyopathy can develop left ventricular hypertrophy for the first time during adolescence when body growth and development are accelerated.[6]

Our patient seems to be an unusual example of an individual who was genetically predisposed to develop hypertrophic cardiomyopathy and who died suddenly before left ventricular mass increased. The only structural evidence of hypertrophic cardiomyopathy at necropsy was cardiac muscle cell disorganisation and abnormal intramural coronary arteries.

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Br Heart J 1990;63:311–3

Dilated and contracted forms of primary endocardial fibroelastosis: a single fetal disease with two stages of development

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Abstract

Left ventricular endocardial fibroelastosis was diagnosed by echocardiographic scanning in a fetus at 20 weeks' gestation. Repeated prenatal examination over the next 20 weeks' gestation showed the development of the left ventricle from a chamber with a dilated cavity to a small cavity with a very thick wall. These findings were confirmed at necropsy and by the absence of other morphological anomalies.

The contracted form of primary fibroelastosis in the fetus must have followed an insult that prevented any further increase in the size of the left ventricular cavity.

The classification of primary endocardial fibroelastosis as either dilated or contracted depends on the size of the left ventricular cavity.[1] So far only a few cases of the contracted form have been reported[2] and these were exclusively in neonates.[3] There are only a few reports of the detection of primary endocardial fibroelastosis in fetuses by echocardiography.[4 5] In these cases, however, the dilated form of the disease only was reported in three infants at 28, 35, and 36 weeks' gestation respectively during a single evaluation. We used similar echocardiographic techniques to detect primary endocardial fibroelastosis in a fetus and follow the course of the disease over 20 weeks.

Case report

A 28 year old primigravida, without risk factors for congenital heart disease, was transferred to our fetal cardiology unit when a four chamber view of the fetal heart was found to be abnormal during routine obstetric ultrasonography at 20 weeks' gestation. Fetal echocardiography showed a dilated and hypotonic left ventricle with a very bright echogenic line over the endocardium which suggested fibroelastosis. The right ventricle was hyperdynamic. Hydrops fetalis was noted (ascites, pericardial and pleural effusions) (fig 1A). The mitral and the aortic valves were normally formed but with poor mobility. Pulsed Doppler assessment of intracardiac flows showed a very low peak velocity and velocity time-integrals through the mitral and aortic valves (fig 1B and C), whereas there was a considerable increase in pulmonary blood flow.

The mother was given digoxin immediately. After 24 hours, she was put on a maintenance dose of 0·5 mg of digoxin. After a few days, the pericardial effusion disappeared but left ventricular contractility remained poor. Two months later, the fetal left atrium seemed to be slightly dilated and the interatrial septum bulged towards the right atrium (fig 2A). At 39 weeks' gestation, echocardiographic evaluations showed a decrease in the diameter of the left ventricular cavity which was associated with a thickening of the free wall with a very echogenic endocardium (fig 2B). At 40 weeks' gestation, a male infant weighing 3·25 kg was delivered vaginally. Apgar scores were 8 and 9 to 1 and 5 minutes respectively. Tests for viral infections were negative. Despite intensive cardiac support, the infant died seven days after birth.

Necropsy showed a thickened left ventricular wall with a small cavity lined by a white layer that was consistent with the diagnosis of endocardial fibroelastosis (fig 2C). The diagnosis was confirmed by microscopical examination (Weigert and trichrome stains). The mitral orifice was smaller than normal (diameter 0 6 cm) but the mital valve leaflets were intact. The aortic valve was bicuspid with thin mobile cusps but the aortic root was only 0·4 cm in diameter. The ductus arteriosus and the foramen ovale were patent.

Discussion

Despite the obvious difference between the dilated and contracted forms of primary endocardial fibroelastosis we think that it is wrong to assume that there are two distinct diseases with different aetiologies. Our patient shows that in a fetus primary endocardial fibroelastosis can start as the dilated stage of the disease and progress to the contracted stage.

Though we did not seek histological evidence of fibroelastosis during gestation, the echocardiographic image of the endocardium was similar to the image at birth when there was histological confirmation of fibroelastosis. Because the fetal ventricles work in parallel, there are two possible courses after the onset of left ventricular failure early in gestation: either the right ventricle efficiently assumes almost

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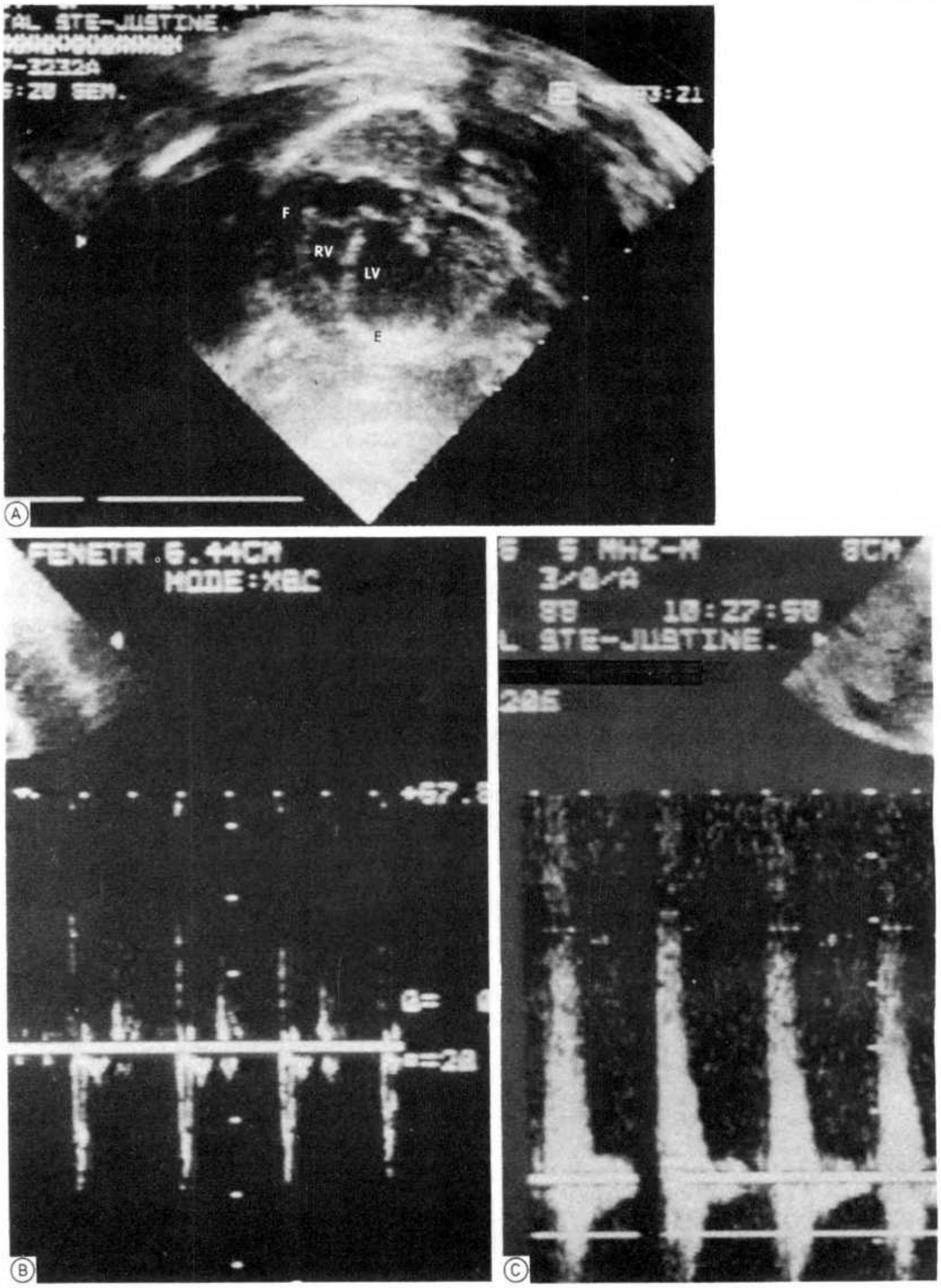

Figure 1 (A) Echocardiographic four chamber view of the heart at 20 weeks' gestation. The left ventricle (LV) was dilated and a bright echogenic line was visible over the endocardium (E). Pericardial fluid (F) was also seen. RV, right ventricle. (B) Blood flow velocity profiles through the mitral and (C) aortic valves. Left ventricular filling occurred chiefly during early diastole.

the entire circulatory load and fetal survival is possible or the right ventricle fails to cope with the new task and the fetus dies. The onset of endocardial fibroelastosis after birth also causes considerable left ventricular failure and because the ventricles now work in series survival depends upon the level of performance of both ventricles.

We first saw our patient at 20 weeks' gestation at an early stage in the development of fibroelastasis. The echocardiographic images were compatible with endocardial fibroelastosis, the left ventricle was hypotonic, dilated, and hydrops fetalis also indicated the failure of the right ventricle. Only rapid treatment of the mother with digoxin prevented the death of the fetus; and evidence of fluid retention disappeared. The ensuing events were predictable—according to the dynamic concept of organic development[6]—the very low blood flow into the left ventricle stopped the growth not only of the left ventricle but also the inflow and outflow valves and the ascending aorta. At birth, after 40 weeks' gestation the dimensions of the left-sided structures were those of a 28 week old fetus. These results support the speculation made by Neill and Ursell[7] that just as the size of the foramen ovale can be used as a marker for intra-atrial flow in utero, so the size of the ascending aorta can be used as an indicator of intrauterine flow through the aortic valve. We believe that the contracted

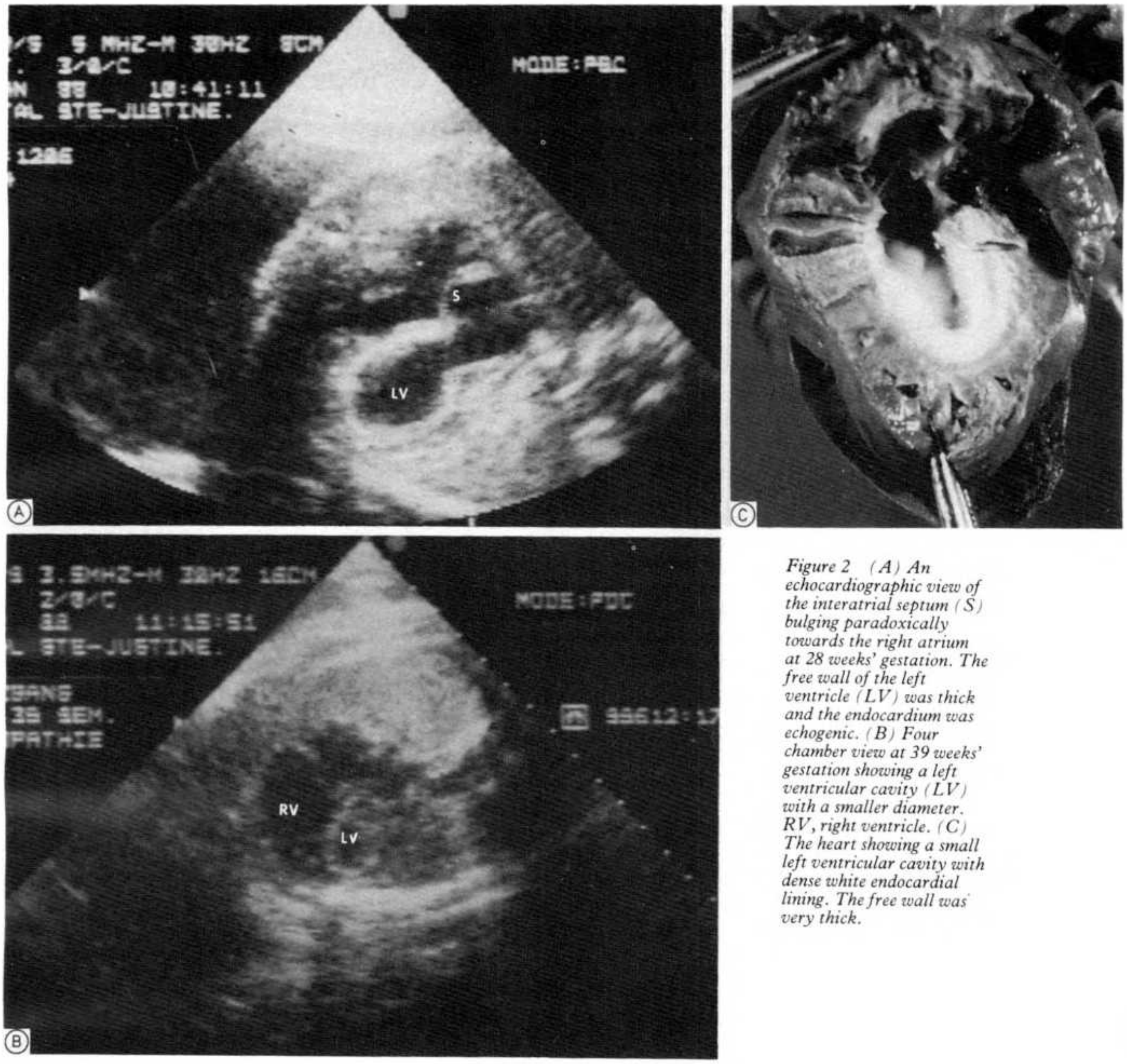

Figure 2 (A) An echocardiographic view of the interatrial septum (S) bulging paradoxically towards the right atrium at 28 weeks' gestation. The free wall of the left ventricle (LV) was thick and the endocardium was echogenic. (B) Four chamber view at 39 weeks' gestation showing a left ventricular cavity (LV) with a smaller diameter. RV, right ventricle. (C) The heart showing a small left ventricular cavity with dense white endocardial lining. The free wall was very thick.

form of primary fibroelastasis evolves from a dilated form of the disease in utero.

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Cor triatriatum dexter: antemortem diagnosis in an adult by cross sectional echocardiography

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Abstract

Cor triatriatum dexter is a rare cardiac abnormality in which the right atrium is subdivided into two distinct chambers. This anomaly is generally attributed to the persistence of the right sinus venosus valve and it is frequently associated with severe malformations of other right heart structures. The antemortem diagnosis of the membrane may be difficult and its presence is often only established at necropsy. In a woman of 56 with Ebstein's anomaly the echocardiographic features of cor triatriatum dexter were examined before and during cardiac catheterisation. These investigations showed the position of the membrane, that there was no gradient between the two atrial chambers, and that there were perforations in the centre of the membrane.

Cor triatriatum dexter or septation of the right atrium to form a triatrial heart is a rare cardiac condition caused by persistence of the embryonic right valve of the sinus venosus.[1 2] It is commonly associated with important abnormalities of other right heart structures. Only those with less severe involvement of the right heart survive childhood.[2-5] Usually the abnormal membrane is first discovered at necropsy, but recent reports suggest the diagnosis can be established antemortem by cross sectional echocardiography.[6 7] We describe a middle aged woman with echocardiographic findings of cor triatriatum dexter and Ebstein's anomaly. The anatomical location of the membrane and its physiological effects were established during a combined echocardiographic and cardiac catheterisation procedure and these results were confirmed at surgery.

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Case report

A 56 year old woman was admitted for assessment of frank cyanosis and clubbing of all digits; these had been progressing slowly for 15 years. She sought medical attention when dyspnoea on exertion and fatigue increased in the two weeks before admission. She did not have palpitation, orthopnoea, chest pain, or oedematous feet.

The jugular venous pressure was elevated and a prominent CV wave of tricuspid regurgitation was noted. A right ventricular impulse was absent. The first heart sound was widely split and soft. The second heart sound was narrowed but not paradoxically split and the pulmonary component was soft. A right ventricular third heart sound was audible as was a II/VI early decrescendo systolic murmur over the lower left sternal border which increased with inspiration. The liver was enlarged and pulsatile.

The chest radiograph showed clear lung fields and a small aortic root. The atria and right ventricle were enlarged. An electrocardiogram showed normal sinus rhythm with a normal PR interval (200 ms), a right ventricular conduction defect without QRS prolongation, and a Q wave in V1 and an S wave in V5 and V6. The left atrium was enlarged (fig 1).

CROSS SECTIONAL AND DOPPLER ECHOCARDIOGRAMS

The situs of the atria and viscera was solitus with concordant atrioventricular and ventriculoarterial connections. A membrane measuring 7 cm in length divided the right atrium diagonally into two chambers forming a superomedial and inferolateral compartment. The membrane was very mobile during the cardiac cycle. During ventricular systole the central portion of the structure inverted towards the roof of the right atrium and during diastole it everted towards the right ventricle (fig 2). The tricuspid valve leaflets were displaced downward into the right ventricular

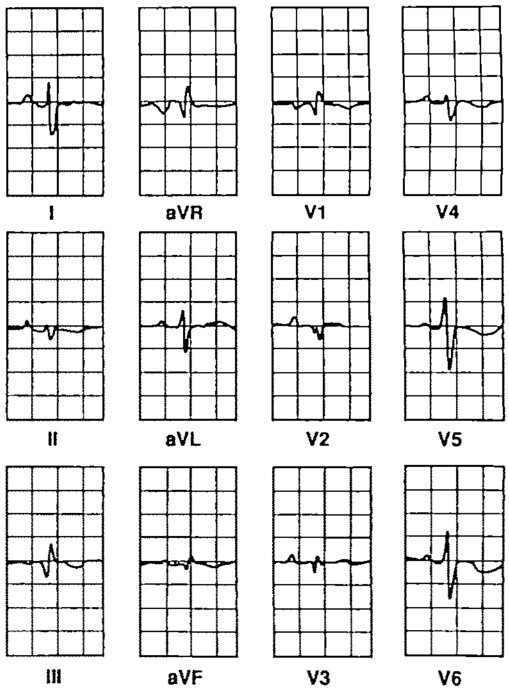

Figure 1 Twelve lead electrocardiogram

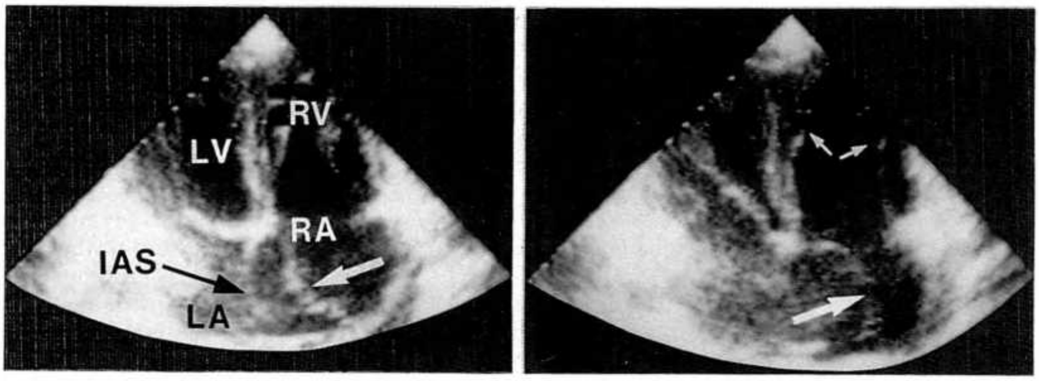

Figure 2 Apical four chamber echocardiogram of the heart during systole (left) and diastole (right). There was a large mobile membrane dividing the right atrium into two chambers (large arrow). The membrane inverted toward the roof of the right atrium during systole and everted toward the right ventricle during diastole. Displacement of the tricuspid valve consistent with Ebstein's anomaly was also apparent (small arrows). IAS, interatrial septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

cavity. No significant obstruction of flow between the two right atrial chambers was detected on the Doppler echocardiographic examination.

On the basis of the physical examination and echocardiographic findings, Ebstein's anomaly and cor triatriatum dexter with no significant obstruction to venous flow was diagnosed.

CARDIAC CATHETERISATION AND ANGIOCARDIOGRAPHY

A combined cardiac catheterisation and echocardiographic procedure was performed. The right femoral artery, right femoral vein, and right internal jugular vein were cannulated. The venous catheters were advanced into the superior and inferior venae cavae. Echocardiography of agitated saline injected into the inferior vena cava showed opacification of the superomedial right atrial compartment and shunting of contrast across the mid-interatrial septum into the left atrium. The contrast also streamed anterogradely into the lateral compartment through multiple areas in the central portion of the right atrial membrane. When contrast was injected in the superior vena cava, the inferolateral right atrial compartment opacified before the superomedial compartment. Retrograde filling through the central portion of the membrane resulted in complete opacification of the medial chamber within two cardiac cycles (fig 3).

The superior vena cava catheter entered the right ventricle through the lateral right atrial compartment. The inferior vena cava catheter was seen in the medial right atrial chamber and easily passed through the mid-interatrial septum into the left atrium. Despite repeated attempts, neither catheter could be passed across the right atrial membrane to enter the opposite atrial compartment. Though the catheters could not be placed through the membrane, as predicted by the earlier Doppler examination, no significant gradient between the two compartments was detected. The right ventricular, pulmonary artery, and left atrial pressures were normal. A bidirectional shunt at the mid-atrial level of 3·25 l/min (right to left) and 0·25 l/min (left to right) was calculated from oximetric measurements and oxygen consumption.

Angiocardiography of the right heart showed the displaced tricuspid valve leaflets, enlarged right atrium and right ventricle, and tricuspid regurgitation. Despite multiple projections, the membrane seen by echocardiography could not be shown during angiography. There were no atherosclerotic lesions of the coronary arteries.

FURTHER COURSE

Surgical intervention for tricuspid valve repair or replacement, closure of the atrial septal defect, and resection of the membrane was

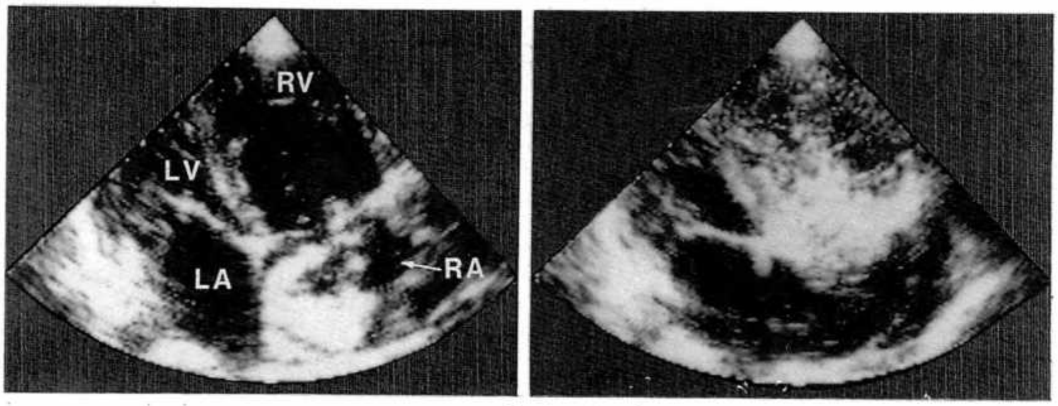

Figure 3 Modified apical four chamber echocardiograms obtained during cardiac catheterisation after injection of contrast through the inferior vena cava (left) and the superior vena cava (right). Injection of contrast through the inferior vena cava showed the initial opacification of the superomedial right atrial chamber and streaming of contrast through the central portion of the membrane into the inferolateral chamber. Injection of contrast through the superior vena cava showed opacification of the inferolateral right atrial chamber. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

recommended. At surgery, a large redundant fibrous membrane with multiple small centrally located fenestrations was found dividing the right atrium into two compartments. The membrane was attached inferiorly from the cristae terminalis to the inferior limbus of the interatrial septum. Anteriorly, the membrane was connected to the right atrium in a similar course. The coronary sinus and inferior vena cava were located to the left of the membrane and the superior vena cava to the right. The septal and lateral tricuspid valve leaflets were adherent to the right ventricular wall. There was an atrial septal defect of the patent foramen ovale type. Primary closure of the atrial septal defect, resection of the right atrial membrane, and insertion of a prosthetic tricuspid valve was performed. After operation the patient's cyanosis resolved and tricuspid regurgitation was no longer present.

Discussion

The membrane seen in the reported cases of cor triatriatum dexter is generally attributed to a persistence of the right sinus venosus valve.[1 2 8] This valve forms during atrial development when the sinus venosus and other structures are progressively incorporated into the developing atria. By 12 weeks' development, the superior portion of the valve is absorbed into the cristae terminalis. The remainder of the right valve typically disappears. However, small remnants of the mid and inferior aspects of the valve occasionally persist, forming the eustachian valve of the inferior vena cava or the thebesian valve of the coronary sinus respectively. Failure of the membrane to regress normally, with subdivision of the right atrium into two distinct chambers, and no separately identifiable eustachian valve is called cor triatriatum dexter.

Necropsy data indicate a high incidence of congenital abnormalities, particularly of the right heart, in patients with cor triatriatum dexter.[2–5] These findings are attributed to the substantial redirection of blood by the right venous valve away from the right ventricle and into the left atrium during embryogenesis.[2 5 7] The most common malformations include an abnormal or underdeveloped right ventricle and pulmonary artery stenosis or atresia. Abnormalities of the tricuspid valve also occur, including Ebstein's anomaly.[9 10]

To our knowledge the attachment of the membrane left of the superior vena cava but right of the inferior vena cava and coronary sinus seen in our patient has not been described before. In a review by Doucette and Knoblich the most common location of the membrane was to the right of the superior vena cava, coronary sinus, and inferior vena cava and the second most common pattern found was when the membrane was to the left of the coronary sinus but to the right of the other two venous vessels.[2] Although the mid and inferior portion of the membrane in our patient most certainly arose entirely from the right sinus venosus valve, the superior aspect may have arisen from the persistence of a skewed septum secundum and the right sinus venosus valve.[2]

Typical findings of cor triatriatum dexter at cross sectional echocardiography were confirmed at necropsy in a neonate.[7] In that patient, there were also two right atrial compartments divided by an extensive membrane with superoinferior attachment. Contrast injection through the inferior vena cava showed complete right to left shunting of blood across a patent foramen ovale. In our patient, echocardiography was also valuable in detecting the membrane and in further defining the presence of Ebstein's anomaly. Using this imaging technique during the catheterisation, we were able to determine the position of the membrane in relation to the great vessels whereas angiography did not show its presence. The echocardiographic procedure before and during catheterisation showed that there was no gradient between the two chambers on the Doppler examination and that there were perforations in the centre of the membrane on the contrast study.

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Br Heart J 1990;63:317–20

BRITISH CARDIOLOGY

Proposals for a new training programme for cardiology

Joint Training and Manpower Group representing the Specialty Advisory Committee and the Cardiology Committee of the Royal College of Physicians of London, and the British Cardiac Society

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1 Introduction

1.1 In recent years the rapid development of the technological aspects of cardiology means that trainees must now acquire not only clinical skills but also considerable expertise in congenital heart disease, the new more interventional cardiac (coronary) care, catheterisation with coronary angiography, arrhythmia control, complex pacemaking, cross sectional echocardiography with colour flow Doppler, nuclear cardiology, and metabolic disease—as well as knowledge of the non-invasive tests undertaken by physiological measurement technicians such as stress testing and ambulatory monitoring. They must also have an interest in epidemiology, prevention, resuscitation, and rehabilitation together with experience in clinical or laboratory research. In addition, some of those planning a career in the specialty require rigorous training in interventional cardiology—namely percutaneous transluminal coronary angioplasty and balloon dilatation of valves. Others may be expected to take an interest in newer imaging methods.

1.2 The distinction between type A and type B cardiologists has also become blurred and indeed outdated. Those who worked exclusively in cardiology used to be designated as type A, whereas type B physicians had responsibility for general medicine with a special interest in cardiology. But the distinction is no longer officially recognised. Rather, there is a range of skills from the interventionalist cardiologist in major centres to the cardiovascular physician in district hospitals who may take some responsibility for general medicine and a share in the emergency "take". But it is now quite common for newly appointed cardiovascular physicians in district hospitals to have one or two weekly sessions at cardiac centres for the purposes of cardiac investigation including catheterisation and coronary angiography. The advantages of these shared appointments are manifold; they include improved liaison, better retention and continuing upgrading of specialised knowledge and practical skills, continuity of patient care, the collaborative provision of facilities for some investigations and treatment (for example, permanent pacing and surgical follow up) that was previously undertaken only in cardiac centres. The benefits to the community in terms of convenience, time, and cost have been great. This tendency for joint appointments is likely to become a universal pattern, though at present geographical considerations and cost constraints sometimes have to be taken into account.

1.3 Training in cardiology has always been onerous but it has become more so as technological advances have become established. Both instruction and experience are necessary and both must be spread over several years if reasonable competence is to be attained in the relevant fields within the specialty. At the same time due regard must be paid to a broad knowledge of general medicine. The Specialist Advisory Committee (SAC) has laid down that one of the years at senior registrar grade must be spent in general medicine and another in research. This remains the policy of the SAC and it is widely supported. The corollary, however, is that the present arrangements leave only two years at senior registrar grade for specialised training in cardiology. At least five years are needed—a figure that is not disputed by those in the specialty who seek to provide the range of skills demanded of them and one that accords with European recommendations for the type of cardiology needed for United Kingdom practice. Exposure to cardiology is likely and desirable during general professional training for all physicians. This, however, cannot be relied upon because rotations vary. Moreover, such experience would not be adequate for the specialist cardiology needed in United Kingdom practice.

1.4 The requirements of the SAC for wide experience during training as a senior registrar on the one hand and the need of specialists to gain adequate experience in the range of cardiology on the other have forced a reappraisal of training recommendations in the light of College and Joint Planning and Advisory Committee (JPAC) proposals. An ad hoc training committee representing the Cardiology Committee of the Royal College of Physicians of London, the British Cardiac Society, and the SAC made new proposals for professional training. These were accepted in modified form by the full SAC. The new format has been discussed within the College and has been approved by the Joint Committee for Higher Medical Training.

2 New SAC proposals for cardiology

2.1 The table shows the scheme. Training in cardiology is envisaged as taking a minimum of nine years from registration rather than the seven years for some medical specialities. The additional time taken for training in specialist cardiology compared with general medicine is recognised in other countries—including now (we understand) within most of Europe.

2.2 The Joint Training and Manpower Group and the SAC regard as essential the ready integration of the new programme with that of general medicine already approved by JPAC. Thus we propose no change in the three years of postregistration general professional training. Trainees should usually have the MRCP (membership of Royal College of Physicians) by this time.

2.3 The major change occurs after that point. We envisage two blocks of three years (similar to that planned independently by our colleagues in cardiac surgery and now approved). Provision of two posts for higher medical training allows for broader experience, flexibility, competitive interchange, and the opportunity for intervening research that we hold to be vital for the survival of academic cardiology. Although we would prefer to lose the term "registrar", it may avoid confusion for the moment if specialty training 1 is called "registrar in cardiology" and specialty training 2 is called "senior registrar in cardiology". Better terms will be introduced in the future.

2.4 Accreditation will follow after five years of specialty training which will come for some individuals after only the second year of block 2 if a year in research is recognised by the SAC. We emphasise that a year in general medicine must be an integral part of this second block to equip trainees for the type of cardiological practice that is most common within the United Kingdom. Those planning a career in interventional cardiology are likely to require an extra year of training, though that will depend on individual circumstances and is not regarded as mandatory.

2.5 The European proposals for the monospecialty section on cardiology (European Union of Medical Specialists) has independently set five years of specialty training as the European standard for hospital cardiologists. Thus our proposals are compatible with the plans for training in medicine as a whole, and match exactly the schemes for cardiothoracic surgery in the United Kingdom and for cardiology within Europe. Though this was fortuitous, the advan-

Proposed training programme

	Mandatory years	*Optional years*	*Notes*
Undergraduate medical training	1 1 1 1	1	BSc or equivalent
Qualifying degree	1		
Preregistration	1		House surgeon/physician
Postregistration general professional training (MRCP by this time)	1		Senior house officer
	1		Registrar
		1 (1)	Research fellow
ENROL *Specialty training 1*	1 1 1 }	↑ or ↓	Registrar
MD by this time		1 (1)	Research fellow
Specialty training 2 ACCREDITATION	1 1 1 }	1 year general medicine	Senior registrar
Additional training		(1)	For interventional cardiology or further GIM if necessary (safety net)

Total of nine to 12 years from registration GIM, general internal medicine.

tages are clear; indeed any scheme in the United Kingdom that did not match that in Europe would have very serious consequences in later years.

2.6 The new training programme proposed by the SAC is set out in detail in the minutes of their meeting of 2 October 1989.

3 Consultant posts within England and Wales

3.1 There are 257 cardiologists for adults in England and Wales,[1] according to a definition accepted within the specialty. This has three requirements: (*a*) a special interest in cardiology; (*b*) appropriate training in the specialty; (*c*) a work pattern with at least 40% of the time devoted to cardiology.

There are in addition 33 paediatric cardiologists, though this number is widely regarded as inadequate (several vacancies have not been filled in recent years because of the shortage of suitably qualified senior registrars).

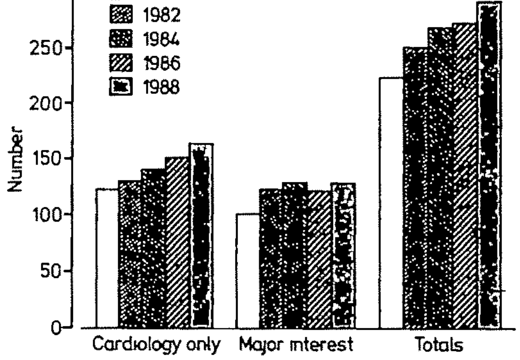
The number of cardiologists overall has grown by 30% over the past nine years (see figure).

3.2 Forty five health districts in England and Wales have no physician meeting the definition above,[1] though a report from the Royal College of Physicians of London and the Royal College of Surgeons of England recommended that every health district with four or more physicians should have one.[2] The British Cardiac Society believes that each large district (over 250 000) needs two.[3]

3.3 In addition, we lag considerably behind even conservative estimates of the need for coronary artery bypass grafting, and this has implications for angiography. Waiting lists for angioplasty are long and growing. No control is exerted on the exposure of cardiologists to the radiation needed for interventionalist cardiology. For staffing levels at major centres to be adequate to meet even the modest targets for intervention made five years ago,[2] and if reasonable targets for treatment and radiation exposure to physicians were met, we would need at least 60 more cardiologists within the centres.

3.4 While we realise that we will not achieve an increase of approximately 100 posts in the foreseeable future (45 as in 3.2, +60 as in 3.3, disregarding the bigger districts), the need for expansion is both clear and urgent. The United Kingdom has six cardiologists per million population, Europe as a whole has 45, and the United States has 60.

Numbers of cardiovascular physicians in England and Wales in 1980–89.



3.5 The growth rate in consultant posts in cardiology has been approximately 3% per annum. Even 5% per annum would leave us in difficulties for a generation or more. We hope that we can achieve at least this modest figure.

4 Senior registrar posts within England and Wales

4.1 The Joint Planning and Advisory Committee has accepted ((SC) 89/38) a need for senior registrars in cardiology to cover an annual growth of seven posts per year with six replacement posts, plus a small allowance for an increased growth that is needed and is indeed already occurring. We therefore retain 56 senior registrars:

$$(7 + 6) \times 4 = 52$$
$$52 + 4 \text{ (additional allowance)} = 56$$

We hope that at least two of these 56 posts will be available for part timers (job share). Ten research posts are included.

4.2 We expect a larger growth rate than at present, and we believe that this will be shown in our next survey due in mid 1990. There has been a rapid turnover in senior registrars in the past two years. The present shortfall of fully trained senior registrars is not restricted to paediatric cardiology: some recent posts have attracted no more than two applicants, and two recent appointees to consultant posts in district general hospitals were not by then accreditable and must complete their accreditation in post. This is not a desirable trend. Moreover, from 1996 we face an appreciable increase in the number of consultants retiring. The numbers of senior registrars should therefore increase to take account of these trends, but the increase will be attenuated if senior registrar posts are to be equated with specialty training 2 which lasts for only three years since the multiplier (see 4.1) becomes three instead of four. We expect that the need for more senior registrar posts on the one hand but the quicker throughput on the other will come close to balancing out. We do not underestimate the importance of this calculation, because the change could affect 12 or 13 posts. The new pattern of training cannot be fully in place until 1996 at the very earliest, and our projected 5% growth rate does suggest that the figures are likely to match fairly closely. The position will be reviewed frequently by ourselves and with the Joint Planning and Advisory Committee.

5 Registrar posts within England and Wales

5.1 If the SAC proposals are accepted—as they have been in principle by the Joint Committee for Higher Medical Training—then protection of posts for specialty training 1 is implied and indeed becomes mandatory because the two 3 year specialty training periods must be closely linked.

5.2 The numbers should be the same as the numbers in specialty training 2 (senior registrars) plus an allowance for wastage. Some individuals will spend only two years in specialty training 2 but others wishing to pursue a career as interventionalists may spend four years. For planning purposes we believe that three years can be taken as the norm.

5.3 Specialties vary in their opinions on wastage at registrar level. We have seen estimates ranging from 0% to 25%. We have no hard data for cardiology. We are aware that training in cardiology is perceived as being valuable for trainees in the pharmaceutical industry, and another source of wastage comes from the many who find the specialty too demanding. We believe our figure for wastage should be set at 15%, with acknowledgement this is only a "best guess".

5.4 The numbers of protected posts for specialty training 1 should therefore be:

$$56 \times 115/100 = 64$$

5.5 The posts in specialty training 1 ("registrar") should be inspected by the SAC to ensure that the structure of the training meets the demands that will be expected both in the United Kingdom and in Europe.

5.6 Our last survey of registrars (cardiology, cardiology plus general medicine, general medicine plus cardiology, research orientated towards cardiology) was carried out in 1987. The total numbers identified were 212 but the numbers were not verified.

5.7 Two points must be emphasised, however, Firstly, many of these individuals were not expecting to make a career in cardiology, and some who did had no realistic prospects of doing so. Secondly, the structure of grades identified in this survey bears little relation to the grade we have called specialty training 1 which will be part of a structured professional training programme.

1 Chamberlain D, Bailey L, Sowton E, Ballantyne D, Boyle D McC, Oliver M. Staffing in cardiology in the United Kingdom 1988 fifth biennial survey. *Br Heart J* 1989, 62.482–7

2 Provision of services for the diagnosis and treatment of heart disease in England and Wales. Third Report of a Joint Cardiology Committee Royal College of Physicians of London and The Royal College of Surgeons of England *Br Heart J* 1985,53 477–82.

3 Cardiology in the district hospital Report of a working group of the British Cardiac Society. *Br Heart J* 1987, 58:537–46.

NOTICES

British Cardiac Society

The Annual General Meeting will take place at the English Riviera Centre, Torquay on 22 to 25 May 1990. The closing date for receipt of abstracts was 19 January 1990.

Cardiac ultrasound

The Fifth Bristol Cardiac Ultrasound Course will be held at the Bristol General Hospital on 17 and 18 July 1990 (cardiac imaging—M mode and 2D) and 19 and 20 July 1990 (Doppler echocardiography—including colour flow). Further details from Dr Peter Wilde, Department of Radiodiagnosis, Bristol Royal Infirmary, Bristol BS2 8HW. Telephone (0272) 230000, Ext 2690.

Computers in cardiology

The Seventeenth International Conference on Computers in Cardiology will take place in Chicago on 23 to 26 September 1990. Inquiries to Dr Robert Arzbaecher, Computers in Cardiology, 10 West 32nd Street, Chicago, IL 60616-3793,USA.

Multiple risk factors in cardiovascular disease

An International Symposium on Multiple Risk Factors in Cardiovascular Disease will take place in Washington, DC on 10 to 12 December 1990. Further information from the Organising Secretariat: c/o Dr Marjorie G Horning, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA, or, for Europe, Fondazione Giovanni Lorenzini, Via Monte Napoleone, 23-20121 Milan, Italy.

Journées Européennes de Cardiologie

Premières Journées Européennes de la Société Française de Cardiologie dans Paris sur 18 et 19 Janvier 1991. Information: Société Française de Cardiologie, 15 rue de Madrid, 75008 Paris, France. Registration: Albine Conseil, 16 boulevard du Parc, 92200 Neuilly sur Seine, France.

Br Heart J 1990;63:321-2

BRITISH
HEART
JOURNAL

Editorial

Percutaneous transluminal coronary angioplasty: what next?

The concept of treating heart disease by means of intravascular catheters was first suggested by Werner Forssmann in 1929.[1] These principles, however, lay dormant for almost half a century until 1978 when Andreas Gruentzig introduced percutaneous transluminal coronary angioplasty.[2] Gruentzig was an imaginative and daring physician who envisaged that coronary revascularisation could be achieved by a minor non-surgical procedure if miniaturised balloons were used to dilate coronary artery stenoses.

Over the past decade the use of percutaneous transluminal coronary angioplasty has grown rapidly. This year about a quarter of a million percutaneous transluminal coronary angioplasty procedures will be performed in the United States alone. Percutaneous transluminal coronary angioplasty can successfully treat single, double, and triple vessel disease and, in properly selected patients, can achieve similar results to open chest surgery. There are now more percutaneous transluminal coronary angioplasty procedures than coronary bypass operations in western countries.

Despite the success of percutaneous transluminal coronary angioplasty during the past decade, several problems remain to be solved. Although most lesions, even the tightest ones and those found in the most remote sites, can be crossed and satisfactorily dilated by modern low profile angioplasty balloons, the short term and long term results remain unpredictable. About one in 20 percutaneous transluminal coronary angioplasty procedures results in occlusion (often abrupt) of the vessel,[3] sometimes requiring emergency surgery. Of those patients who have an initially successful percutaneous transluminal coronary angioplasty, one in three has only temporary relief of symptoms; the lesion, for reasons that are not yet wholly known, recurs within a few weeks or months.[4] In consequence, about 40% of patients undergoing percutaneous transluminal coronary angioplasty will not achieve a long term benefit from this "minor" procedure.

In the early years the enthusiasm for revascularisation of the myocardium via the natural routes of the circulation and without the need for surgery overwhelmed any scepticism. With increasing experience, however, many cardiologists became concerned about the high rate of restenosis and the need for repeated dilatations. Not infrequently three, four, or more dilatations would be required before recurrence was finally prevented, and this reduced substantially the effectiveness of this otherwise elegant procedure. Health authorities became aware of the cost of repetitive interventions, patients worried about excessive morbidity, and physicians became frustrated. Various solutions to these problems were proposed. Because thrombosis was believed to be an important factor, several expensive trials of different antithrombotic regimens were undertaken. Although these agents were effective in reducing the acute problems, none reduced the restenosis.[5] Anti-inflammatory drugs, intended to reduce tissue proliferation, were also ineffective.[6] The possibility that vasomotor tone affected the genesis of restenosis led to the use of calcium channel blockers, but no significant reduction of restenosis was shown.[7] The results of giving dietary supplements of fish oil were conflicting. Currently, several large clinical trials with different enzyme inhibitors are either under way or about to be launched.

Mechanical approaches have included longer inflations and over-inflations intended to optimise the initial result, the removal of plaque material with the help of complex catheter systems (fluid jets, drills, shavers, lasers), and the permanent implantation of miniaturised endoluminal support devices (stents) made of metal or other biologically compatible substances.

Though removal of atheromatous material gives a fascinating insight into the histological composition of restenoses, it does not seem to reduce the rate of restenosis.[8] Atherectomy may help to direct further research but so far it has not improved results. Laser ablation too has been beset by technical and safety problems for many years; preliminary clinical observations indicated few acute problems but the restenosis rate, at least for lasers that produce local heat, was disappointingly high.[9 10] The restenosis rates after excimer laser ablation are as yet unknown.

The results with stents are more encouraging. If the acute phase passes without thrombosis then restenosis seems to be rare.[11 12] The incidence of restenosis varies slightly according to the type of stent implanted, but can be well below the usual 33%. For self expanding mesh stents we found restenosis rates of under 10% in native arteries and only slightly higher in bypass grafts,[13] which without stenting tend to produce many restenoses.[14] If the incidence of percutaneous transluminal coronary angioplasty procedures remains stable, such a reduction in restenosis rate would produce substantial savings—about 2 billion dollars per year in the United States. Stents were also effective in the management of acute occlusion after percutaneous transluminal coronary angioplasty[15] and restenosis is rare in patients who have stents for this indication.

Physicians are reviewing their attitudes to percutaneous transluminal coronary angioplasty. Marketing reports indicate that the growth of percutaneous transluminal coronary angioplasty in the United States is slowing; for 1989 the increase over 1988 is estimated to be 9%—a considerably smaller increase than in earlier years. The reasons for this change are complex; certainly if the demand for percutaneous transluminal coronary angioplasty is about to level out competition among centres should encourage better quality control and should deter operators with a weak performance record. This change in attitude, however, largely results from the increasing appreciation of the limitations of percutaneous transluminal coronary angioplasty. The results of studies such as TIMI II have clearly added to this trend.[16]

For the first 10 years of experience with the procedure, percutaneous transluminal coronary angioplasty was a rather crude way of treating diseased arteries. I am convinced that the best is yet to come. In future percutaneous transluminal coronary angioplasty is likely to focus on hybrid therapeutic strategies: pressure remodelling with balloons; removal of atherosclerotic material if necessary (possibly under angioscopic vision) by cutters, drills, or lasers that analyse their target before destroying it; and last but not least, supporting the artery with non-thrombogenic, possibly biodegradable stents. These stents must be easily implantable and must limit proliferation. The technology exists: we have to direct our imagination and research towards the choice of implantable materials and local delivery systems for drugs that modulate the control of vasomotor tone and promote optimal healing of the vessel wall. Most importantly, we need to identify and eliminate the stimuli that lead to atherosclerosis and restenosis.

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Br Heart J 1990;63:323–4

Editorial

Restrictive cardiomyopathy

Several cardiomyopathies show restrictive haemodynamic characteristics at some stage of their development. At earlier stages arrhythmias may occur, whereas later some progress to a haemodynamic picture that is reminiscent of dilated cardiomyopathy. During their restrictive phase it can be difficult to distinguish these cardiomyopathies from constrictive pericarditis and restrictive-obliterative endocardial disease (Loeffler's endocarditis and endomyocardial fibrosis). With a few exceptions (for example, haemochromatosis), there is no specific treatment for restrictive cardiomyopathies. The main reason for making an accurate diagnosis is to exclude constrictive pericarditis which is eminently curable. Also some patients with endocardial disease benefit if the abnormal endocardium is stripped.[1] In addition, some histological appearances are definitely associated with inherited conditions (for example, Fabry's disease) and others are also probably familial (for example, myocyte hypertrophy (our unpublished observations)) and genetic counselling may be indicated.

By restriction we mean that systolic function is less affected than diastolic function and in particular that there is an abnormality of filling rather than of relaxation. One description of restrictive haemodynamic function is "rapid completion of filling of a poorly complaint ventricle in early diastole, with little or no further filling in late diastole".[2] Though there is poor compliance of the ventricles the peak filling rate is higher than normal, possibly as a result of augmented ventricular diastolic suction.[3] The situation is thus analogous to pericardial disease causing constriction or tamponade. But individuals with dilated and hypertrophic cardiomyopathies can also show similar haemodynamic characteristics,[2] as do some individuals with normal hearts if their filling pressures are raised. Moreover, not everyone with restrictive filling shows rapid completion of filling in early diastole. In some cases treatment with diuretics can cause a relatively low filling pressure at investigation. Also, some individuals with a poorly compliant ventricle with normal volumes but high filling pressures and one of the histological appearances characteristic of restrictive cardiomyopathy can show rapid completion of ventricular filling in early diastole whereas others with a similar histological appearance show gradual slow ventricular filling throughout diastole. Both filling patterns may be seen in amyloidosis,[3, 4] but we have also seen them in restrictive cardiomyopathies with other histological appearances.

Usually patients with restrictive cardiomyopathy have normal ventricular volumes but raised filling pressures. As a result in restrictive cardiomyopathy atrial dimensions are often increased; this is rarely the case in constrictive pericarditis. In both constriction and restriction there is characteristically rapid completion of ventricular filling in early diastole so that the ventricular diastolic waveform has a dip and plateau (square root sign) configuration, but this is not always true.[5, 6] Filling and the ventricular diastolic waveform are affected by heart rate,[3, 6] degree of hydration, and stage in the disease process[3, 4] so that in some individuals filling is more gradual. The left and right ventricular end diastolic pressures are usually nearly identical in constrictive pericarditis but often the left ventricular end diastolic pressure is at least 5 mm Hg higher than the right in restrictive cardiomyopathy.[6-8] Unfortunately this is not an absolute sign. Diastolic ventricular pressure can differ if there is localised constriction or a coincident cardiac abnormality in patients with pericardial disease. Moreover, some patients with restrictive cardiomyopathy maintain a constant relation of ventricular diastolic pressures even when filling pressures are altered.

We and others[8, 9] believe that endomyocardial biopsy is a useful method of distinguishing restrictive cardiomyopathies from constrictive pericarditis and endomyocardial fibrosis. A specific condition such as iron storage disease, Fabry's disease, sarcoidosis, or glycogen storage disease may be diagnosed.[10] Though non-specific histological features, such as interstitial fibrosis and (according to our unpublished observations) myocyte hypertrophy are common, many patients with restrictive haemodynamic function have amyloidosis. This condition cannot be excluded purely on the basis of light microscopy.[8] Electron microscopy of myocardial tissue can confirm the diagnosis when light microscopy is negative[8] though care should be taken to distinguish between recently formed perimyocyte collagen and amyloid. The presence or absence of amyloid deposits in other organs is not absolutely predictive of cardiac involvement.[8, 11, 12]

Cardiac amyloidosis may present in several ways. Arrhythmias or angina despite angiographically normal coronary arteries can precede the onset of cardiac failure. Myocardial ischaemia may be the result of small vessels being affected by amyloidosis,[13] or of the great degree of ventricular wall thickening seen in this condition.[14, 15] Amyloidosis may also mimic hypertrophic cardiomyopathy because it can cause asymmetrical septal thickening.[13, 16] The ventricles can be dilated with reduced ejection fractions in the later stages of the disease.[17-19] Sometimes the individual patient with amyloidosis can have features intermediate between all three types of cardiomyopathy—for example, asymmetrical septal thickening, angina, heart failure, abnormal diastolic function, and a reduced ventricular ejection fraction.

Technetium-99m pyrophosphate scintigraphy has been suggested by some to be a useful adjunct in the diagnosis of amyloid heart disease,[14-21] as has the presence of a granular sparkling myocardial appearance on echocardiography.[14] Frequent false negative results, however, impair the sensitivity of these techniques.[16]

Patients with restrictive cardiomyopathy occasionally have normal endomyocardial biopsy specimens.[7] When this happens a diagnosis of constrictive pericarditis may have been missed, though patchy infiltration, for example by sarcoidosis, is possible.[22] Other methods should always be used to exclude the presence of constrictive pericarditis if histological examination shows normal myocardium or is inconclusive. The consequences of missing a diagnosis of constriction can be serious. Whereas important atrioventricular valve regurgitation is much more common in restrictive cardiomyopathy than in pericardial constriction, this clinical sign is unhelpful in individual patients. Valve regurgitation and pericardial constriction can coexist[23, 24] particularly when rheumatic carditis is the cause. Pericardial constriction often occurs without calcification in rheumatic disease. Indeed, pericardial constriction was seen without any detectable pericardial calcification on chest x ray in 30–70% of cases.[25–27] Pericardial thickening on echocardiography is also unreliable.[27–29] Computed tomography and magnetic resonance imaging may be better methods of detection.

There were significant differences between the indices derived by digitised M mode echocardiography (particularly the peak rate of thinning of the posterior wall during early diastole) from patients with constrictive pericarditis and restrictive cardiomyopathy.[27] Unfortunately, overlap of values between the two groups means that these statistically significant differences do not produce a clinically useful discriminant. Recent observations suggest that Doppler echocardiography may prove to be a highly sensitive method of distinguishing between constriction and restriction.[29] The respiratory variation in left ventricular isovolumic relaxation time and peak early mitral flow velocity distinguished clearly between constrictive pericarditis and restrictive cardiomyopathy. Unfortunately the number of patients in this study was small and it has some limitations, which the authors recognised. These observations need to be confirmed in a larger study.

When doubt remains about the presence of constrictive pericarditis or restrictive cardiomyopathy exploratory cardiotomy should be performed.[27] Even then removal of a thickened pericardium may not cure the patient. Restrictive cardiomyopathy and constrictive pericarditis can coexist if they have a common cause, such as radiation fibrosis.[29 30]

Though pericardial constriction and endomyocardial fibrosis can be treated by pericardectomy and endocardectomy,[1] most causes of restrictive cardiomyopathy have no specific treatment. Patients with iron storage disease may benefit from venesection or chelation of iron.[31] Specific medical treatment for cardiac amyloidosis does not increase life expectancy.[32]

Non-specific treatment for heart failure should be used with caution in patients with restrictive cardiomyopathies. Because these patients require a high filling pressure to maintain their cardiac output, the results of using diuretics or vasodilators may be deleterious. These include severe hypotension and cardiogenic shock. There are also anecdotal reports of extreme sensitivity to cardiac glycosides and β blocking drugs.[32 33]

The reports of prognosis in patients with restrictive cardiomyopathies are highly variable. This is because most reports are of small, heterogeneous groups of patients. The cause of the cardiomyopathies and the severity of the heart failure at the time of presentation, as well as concomitant events (such as embolic phenomena and arrhythmias) will affect prognosis. In a large series of patients with amyloidosis, the median survival of patients with heart failure was 6 months from onset of symptoms.[34] In patients with primary restrictive cardiomyopathy, one group reported no deaths in a series of nine patients followed up for 16–42 months.[7] The experience of others has been less favourable.[32]

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EPIDEMIOLOGY

Exercise in leisure time: coronary attack and death rates

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Abstract

Nine thousand three hundred and seventy six male civil servants, aged 45–64 at entry, with no clinical history of coronary heart disease, were followed for a mean period of 9 years and 4 months during which 474 experienced a coronary attack. The 9% of men who reported that they often participated in vigorous sports or did considerable amounts of cycling or rated the pace of their regular walking as fast (over 4 mph, 6·4 km/h) experienced less than half the non-fatal and fatal coronary heart disease of the other men. In addition, entrants aged 55–64 who reported the next lower degree of this vigorous aerobic exercise had rates less than two thirds of the remainder; entrants of 45–54 did not show such an effect. When these forms of exercise were not vigorous they were no protection against the disease, nor were other forms of exercise or high totals of physical activity per se. A history of vigorous sports in the past was not protective. Indications in these men are of protection by specific exercise: vigorous, aerobic, with a threshold of intensity for benefit and "dose response" above this threshold, exercise that has to be habitual, and continuing, which suggests that protection is against the acute phases of the disease. Those men who took vigorous aerobic exercise were demonstrably a favourably "selected" group; they suffered less of the disease, however, whether at low risk or high by the several risk factors that were studied. Men with exercise-related reduction in coronary heart disease also had lower death rates from the total of other causes, and so lower total death rates than the rest of the men.

Initial observation that middle aged men in jobs that require physical activity have a lower incidence of heart attack than comparable men in sedentary jobs[1] prompted the hypothesis that high totals of physical activity in leisure time would protect sedentary workers.[2] Prospective survey of such men in the civil service, however, did not corroborate this. Only those reporting vigorous aerobic exercise showed substantially less coronary heart disease. Vigorous exercise included the most strenuous activities of these men, so it was well above their normal levels of activity, and it was further defined as being liable to entail peaks of energy expenditure of 7·5 kcal/min, 31·5 kJ/min (say $>$ 6·0 resting equivalents (METS) and $>$ 65% of maximum oxygen uptake). This is usually adequate, it may be postulated, to produce and maintain a cardiorespiratory training effect in such a population.[3-8]

It is hazardous, however, to generate a new hypothesis post hoc from the same data set. Furthermore, in an admittedly different population of American men, though players of vigorous sports showed the lowest coronary rates, there was some protection also in a minority who took less intense aerobic exercise, and thus had high totals of leisure activity ($\geqslant$ 2000 kcal per week)[9 10] (and Paffenbarger *et al*, 1988, personal communication). As well as questions about the kind of exercise that is protective against heart disease, of a postulated threshold for benefit and, in general, how to represent physiological "training" in a population study, many other issues must be considered. These are: the effects of advancing age; the possibility of other causes of death occurring among those protected, or being diagnosed instead; the interaction of exercise with other behaviours, and with standard risk factors; the multiplicity of possible mechanisms for the protection now being proffered—and the abiding question of possible self selection for exercise and against heart attack. In the hope of shedding further light on such issues a prospective survey was launched.

Subjects and methods

In the autumn of 1976 all male executive officers aged 45–64 in post in the Department of Health and Social Security and in Inland Revenue throughout Britain were invited to participate. These officers are (or were) a white collar middle management grade, a narrow though not untypical, homogeneous and stable educational/occupational/economic band of the middle class, engaged in sedentary or physically light office work. Eighty two per cent of the men readily agreed, yielding 9376 respondents after exclusion of the 6% with a history or record of clinical coronary heart disease. They constitute the study cohort who were followed until 30 April 1986. They were asked to give a detailed account of physical activity in the previous 4 weeks in a questionnaire designed (after pilot interviews) to be comparable with the national data of the General Household Survey[11,12] (and personal communication, OPCS, 1979). The intensity and energy demands of the activities reported were derived as best we could from physiological studies[3,4,8,13,14] to provide the broad gradings required.

A 25% random sample of the completed questionnaires was drawn, coded independently and in full by two clerical officers, and checked and reconciled, as occasionally required, by MGE; this sample was multiplied by four to estimate our total population data.

As before[3,4] the Occupational Health Service of the Civil Service reported, in confidence, major morbidity among all men (episodes of sickness absence over 30 days in one year or within two consecutive years, with their certified cause; and episodes of any duration certified as cardiovascular disease) together with the man's medical history. The diagnoses thus were derived from information provided by the men, by the men's general practitioners, and by weekly certificates from National Health Service hospitals. In a few instances where no categorical diagnosis had been made, we ourselves checked with the doctors and hospitals for the clinical details. There were also a small number of retirements on medical grounds. These men normally retire at 60, so we disregarded morbidity after 60. All this yielded 202 non-fatal cases during the follow up: these were the first recognised clinical episodes of coronary heart disease in men aged 45–59; in most these were "coronary thrombosis/acute myocardial infarction" with a few cases of angina pectoris or coronary insufficiency.

Deaths were notified by the departments and the Paymaster General; all men in the survey were also flagged at the National Health Service Central Registry which routinely sent copies of death certificates. All these were processed by the Medical Division of the Office of Population Censuses and Surveys and those classified as coronary heart disease (ICD 410–414) as the main or underlying cause of death (plus two deaths overseas) in men not already accepted as cases of coronary morbidity were admitted as 272 fatal cases. These were spread through the cohort aged 45–64, observed prospectively for 9·3 years; the highest age at death was 73 years.

These deaths together with the non-fatal cases, 474 in all, in 87 563 man-years' observation (44 933 at 45–59 and 42 630 at 60–73) make up our composite age standardised coronary attack rate of 5·41 per 1000 man-years, with the non-fatal cases being aged 45–59 at the event and the fatal 45–73. In the analysis of mortality it seemed more rigorous to include all coronary deaths during the observed follow up. This added 17 deaths in second or later episodes to the 272, too few though to make a material difference.

The questionnaires of all the cases were coded in the same way as the cohort sample.

This therefore is a case-cohort study[15] permitting estimation of man-years observed and the calculation of population rates, not merely individual relative risks (see Appendix).

PHYSICAL ACTIVITY IN LEISURE TIME

This takes three forms in these men: (*a*) sports and games, keep fit/callisthenics; (*b*) moving about—walking, cycling, stair climbing; (*c*) manual work in and about the house and garden and on the car—that is "work" in the general sense not the physiological term.

Previously, a cluster of frequent/"vigorous" (as defined) aerobic, dynamic exercise in (*a*) and (*b*) was associated with much lower coronary incidence rates (first clinical episodes). This became the main hypothesis to be tested. At the same time, the five components of the cluster—vigorous sports, daily or near daily keep fit, fast walking, considerable amounts of cycling, the extreme of stair climbing—were tested individually. More tentatively, we tested the hypotheses that much vigorous manual work, which previously had shown a limited association with incidence, would also provide some protection and that other physical activity would not be protective.

Results

EXERCISE AND RATES OF CORONARY HEART DISEASE

Sports and games

Table 1 breaks these down into "vigorous",

Table 1 Playing of sports and games and the attack rate of coronary heart disease in male executive grade civil servants (rates per 1000 man-years)

	*(A) Vigorous sports**			*(B) Non vigorous†*		
	Coronary attacks (1976–86)			*Coronary attacks (1976–86)*		
Episodes in previous 4 weeks reported at entry in 1976	*Cases*	*Man-years*	*Age standardised rate*	*Cases*	*Man-years*	*Age standardised rate*
None	413	72 282	5·8	310	58 326	5·4
1–3	37	7 786	4·5	85	14 190	5·9
4–7	17	4 146	4·1	52	8 532	5·9
8–11	7	3 349	2·1	19	5 322	3·5
≥12				8	1 193	6·8
Total	474	87 563	5·4			
		$p < 0·005$			$p > 0·05$	

Men aged 45–64 at entry in 1976 with no history or record of coronary heart disease followed to 1986. Attack rates include all recognised first coronary events, non-fatal (202 at 45–59 years) and fatal (272 at 45–73 years of age).
*Liable to reach energy output of 7·5 kcal (31·5 kJ) per minute
†Results were similar when men also reporting vigorous sports are excluded.
All significance tests reported are for trend,[16] although heterogeneity tests were also carried out, and allow for sampling of the population (see Appendix).
The few men with no or spoiled records are included in None.

reported by 17·5% of the men, and "non-vigorous" sports, which were twice as common. The contrast between (A) and (B) is plain, corroborating the hypothesis of a threshold of intensity for effectual exercise. There is some indication too in (A) of a "dose response" with frequency; the finding with 8 or more episodes of exercise—that is at least twice a week on average—reported by 3·8% of the men, is the strict test of the hypothesis.

Swimming was the most popular vigorous sport; there were also appreciable numbers of men jogging, playing badminton, tennis, football, and hockey (including coaching and refereeing), hill climbing, and rowing. Dancing, golf, and table tennis were the commonest non-vigorous sports.

Validity: intensity of exercise. We asked participants about symptoms induced by activity to see whether exercise classed as "vigorous aerobic" by our simple methods did indeed demand greater exertion. These data and the many issues they raise will be reported elsewhere. But we certainly found that the men reported being "out of breath" more often with sports that we deemed to be vigorous.

Previous history of exercise. Participants were asked whether they had played vigorous sports and stopped before entry to the survey. Men who reported such sports at entry in 1976 often replied that they had engaged also in other such sports in the past, illustrating "self-selection" for vigorous exercise. More interestingly, in men reporting no vigorous sports in 1976 there was no relation between coronary attacks during the follow up, 1976–86, and earlier playing of vigorous sports:

Vigorous sports previously played by men reporting none in 1976:

	Cases	*Rates* 1976–86
Played none previously	292	*5·9*
Played up to 25 years of age	42	*5·1*
Played up to 30 years of age	33	*5·1*
Played up to 40 years of age	36	*6·5*
Played past 40 years of age	8	*5·2*

The results are the same even if only the most vigorous sports are considered—athletics, rugby, running, squash, boxing, and the like. The implication is that continuing current exercise alone protects against the disease. This independently corroborates and amplifies the American observation.[9] The observation argues, too, against a critical genetic component in the exercise effect.

Consistency in behaviour pattern. The hypothesis implies that the protective behaviour is habitual. Vigorous aerobic exercise was found to be a particularly stable trait in the short term and when we compared reports in the present survey with those in the first.[3 4] There is a further confirmation from a follow up performed for us by the Paymaster General in 1982–84 of the 40% of our participants aged 55–64 who had by then retired; 92% of them responded. Each man reporting vigorous sports in 1976 was matched randomly by age, smoking, and length of follow up with three controls who in 1976 had reported no such activities. Half (51%) of the former reported vigorous sports again in 1982–84 and a further 19% reported other vigorous aerobic exercise, mainly keep fit. The proportions in the controls were 13% and 9·5% respectively.

MOVING ABOUT

We asked the men for information on how many minutes they had spent *walking* to and from work and on other regular walking outside the home in the past week. The quantity of walking (table 2A) was not associated with any decline in attack rates—for example, the figure of 6·0 with average walking of over an hour a day. Participants were also asked to grade the usual or average pace or speed of their regular walking.[17 18] To test the threshold hypothesis, "fast" was defined as "over 4 mph" (6·4 km/h). Table 2B shows a trend in the rates of disease and there is a particularly low rate in the 2·6% of men claiming to be fast walkers. In table 2C, combining intensity and quantity, there is a somewhat reduced attack rate in those reporting over half an hour a day of "fairly brisk" walking. This, which is the grade below "fast" walking and perceived to be faster than "normal", is deliberately strenuous, it may be postulated, vigorous, and the rate may be another indication of a dose response. The "strollers", 11% of the men, reported many mobility problems, and they were generally

Table 2 Regular walking and the attack rate of coronary heart disease (1976–86) in male executive grade civil servants (rates per 1000 man-years)*

(A) Duration			*(B) Pace*			*(C) Duration and pace*								
Hours of regular walking in past week	*Coronary attacks*		*Usual average pace†*	*Coronary attacks*		*Hours in past week*	*Stroll*		*Normal*		*Fairly brisk*		*Fast*	
	Cases	*Rates*		*Cases*	*Rates*		*Cases*	*Rates*	*Cases*	*Rates*	*Cases*	*Rates*	*Cases*	*Rates*
None‡	51	*5·0*	"Stroll at an easy pace"	78	*7·9*									
3·5	317	*5·6*	"Normal"	222	*5·5*	≤3·5	64	*7·3*	163	*5·2*	88	*5·7*	2	*(1·5)*
7	85	*5·1*	"Fairly brisk"	120	*4·8*	>3·5	14	*12·0*	59	*6·9*	32	*3·4*	1	*(0·9)*
7	21	*6·0*	"Fast (over 4 mph)"	3	*(1·3)*									
Total	474 $p > 0·05$		$p < 0·05$											

Men aged 45–64 at entry in 1976.

*Walking to and from work and other regular walks outside the home. Reported at entry.

†Self-rating at entry of "usual" pace of regular walking Excluding the "None" (51 cases).

‡Activities of less than 5 minutes are disregarded throughout; the numbers for "None" therefore are an overestimate.

All inclusive rates are age-standardised.

Rates based on less than 5 cases are shown in parentheses throughout.

Table 3 Recreational "work" and the attack rate of coronary heart disease (1976–86) in male executive grade civil servants (rates per 1000 man-years)

Hours in previous 4 weeks†	(A) Heavy work*				(B) Moderate				(C) Light			
	Gardening		Other		Gardening		Other		Gardening		Other	
	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates	Cases	Rates
None	227	5·7	253	5·3	179	5·2	123	4·9	213	5·7	119	5·1
1–3	175	5·4	155	5·7	261	5·6	213	5·5	206	5·1	265	5·2
4–7	42	4·9	21	4·6	30	5·2	50	5·3	38	5·8	44	6·7
8–11	15	5·4	29	5·3	4	(5·4)	51	5·7	8	4·2	31	6·9
⩾12	15	4·3	16	5·9	0	0	37	6·5	9	5·2	15	5·9
Total	474		474									

*Liable to reach energy output of 7·5 kcal (31·5 kJ) per minute.
†Reported at entry.
$p > 0{\cdot}05$ throughout.

vulnerable (for example 15% of them gave a history of "subclinical" cardiovascular disease); this simple self-assessment is remarkedly predictive of heart attack.

"Vigorous" *cycling* was defined as an amount previously found to be associated with a lower incidence: at least an hour per week in the round trip to work or at least 25 miles of other cycling in the previous week. Cyclists of course often reported both forms. In the 3·5% of men who reported vigorous cycling the attack rate was much lower: eight cases, 2·6 per 1000 man-years. There was also some reduction with less cycling: 14 cases and 4·5 per 1000 man-years ($p < 0{\cdot}03$), indicating perhaps that any habitual cycling in these middle aged men usually entailed enough effort for benefit.[19] But as only 7% of the men cycled numbers are too few for proper analysis.

KEEP FIT AND STAIR CLIMBING

There was no association with age-standardised coronary rates in these two remaining types of vigorous aerobic exercise which previously were found to be protective. The attack rate with keep fit/callisthenics at least 5 times a week was 5·6 per 1000 man-years. Men climbing the most stairs (⩾500 each day) had an attack rate of 5·4, which was in the middle of the observed range of rates (4·7 to 6·2 per thousand man-years) by total number of stairs that were climbed.

RECREATIONAL "WORK"

Most of these men lived in a suburban house with a garden: 91% reported gardening, Do It Yourself also was very popular, and a wide range of "jobs", hobbies, and crafts were reported. Table 3 divides this productive activity into gardening and the rest. It begins (A) with the most arduous work, that is "vigorous" as defined (as liable to entail an energy output of 7·5 kcal/min)—for example, digging, tree felling, concreting, and replacing worn parts of the car. Seventy per cent of men reported doing some of this type of work. "Moderate" work, approximately 5 but < 7·5 kcal/min, was mostly lawn mowing by hand or painting and decorating, and polishing the car; 71% reported doing moderate work. "Light" jobs (C)—for example raking and pruning, and repair of home appliances—were equally popular. Table 3 shows that whatever the quantity or intensity of recreational work it had no effect on the rates of coronary heart disease.

THRESHOLD: DOSE RESPONSE

The men were now ordered by the exercise they reported, and in terms of the main hypothesis (table 4).

Group 1 consists of those reporting frequent/intense, vigorous aerobic exercise—that is, vigorous sports at least twice a week, and/or "fast" walking, and/or considerable cycling.

Group 2 are the men reporting the next lower degree of such exercise which was either not so frequent (that is, vigorous sports at least once but less than twice a week, and/or less cycling) or not so intense (that is "fairly brisk" walking for over half an hour a day).

Group 3 was made up of those men taking residual vigorous aerobic exercise—that is, occasional sports (1–3 episodes in the 4 weeks), or shorter "fairly brisk" walking.

Group 4 are the men reporting no vigorous aerobic exercise.

The upper panel of table 4 shows the trends in coronary disease across groups 1–4 for overall attacks and mortality (and similarly in the non-fatal cases, by subtracting "mortality" from "total attack rate"). Group 1 men had strikingly low rates throughout ($p < 0{\cdot}001$).

In those who were 45–54 at entry, the composite group 2 rate was not reduced and not significantly different from that in groups 3 and 4, while among entrants of 55–64, the men in group 2 (19%) had a significantly lower rate of disease than groups 3 and 4 ($p \simeq 0{\cdot}01$). Equally interesting, the two items of the original "vigorous aerobic" cluster that did not qualify for group 1 (frequent keep fit and much stair climbing) were now associated with reduced coronary rates of 2·7 and 3·5 per 1000 man-years in these older men, and they have therefore been included with group 2; both activities are likely to be more variable and liable to be less intense on average than the exercise in group 1. In group 3 there was some continuation of a favourable trend in rates in the older men. These therefore showed a dose response to the intensity of vigorous aerobic exercise. A threshold effect alone is seen in the younger men.

Validity of the diagnosis of coronary heart disease. As a check the 135 fatal cases certified by a coroner (medical examiner) after necropsy as coronary heart disease were sorted into the four exercise groups. The trend of the age standardised rates (45–64) for these cases is similar to the experience overall: 0·39, 1·4, 1·7, 1·7 in groups 1–4 respectively ($p < 0{\cdot}001$).

Table 4 Vigorous aerobic exercise, attack rate, and mortality of coronary heart disease (CHD) (1976–86) in male executive grade civil servants (rates per 1000 man-years)

CHD experience 1976–1986	*Group 1 (frequent vigorous aerobic exercise)*	*Group 2 (next lesser degree of this)*	*Group 3 (residual vigorous aerobic exercise)*	*Group 4 (no vigorous aerobic exercise)*	*Totals*	*p*
			Ages 45–64 at entry			
Attack rate·						
Man-years observation	8062	13 185	22 157	44 159	87 563	
Cases	18	62	122	272	474	
Rates	*2 2*	*4·7*	*5·4*	*6 3*	*5 4*	<0 0005
Relative risk %	35	76	85	100		
(95% CI)	(21–57)	(56–101)	(68–108)			
Mortality·						
Cases	10	39	71	169	289	
Rates	*1 3*	*2 9*	*3 3*	*3 7*	*3 3*	<0 005
RR %	34	78	88	100		
(95% CI)	(18–66)	(54–112)	(66–117)			
			Ages 45–54 at entry			
Attack rate:						
Cases	10	38	77	125	250	
Rates	*2 1*	*6 3*	*6·1*	*6 5*	*5 9*	<0 025
RR %	33	97	94	100		
(95% CI)	(17–64)	(66–144)	(69–128)			
Mortality:						
Cases	3	20	34	52	109	
Rates	*0 63*	*3 3*	*2·7*	*2 6*	*2·6*	>0·05
RR %	24	125	101	100		
(95% CI)	(7–78)	(73–214)	(65–158)			
Total No of men	508	776	1216	2052	4552	
			Ages 55–64 at entry			
Attack rate						
Cases	8	24	45	147	224	
Rates	*2·3*	*3·3*	*4·5*	*5·9*	*5 0*	<0 001
RR %	39	56	78	100		
(95% C)I	(19–82)	(36–88)	(54–111)			
Mortality:						
Cases	7	19	37	117	180	
Rates	*2 1*	*2·6*	*3 8*	*4·6*	*4 0*	<0 005
RR %	45	56	82	100		
(95% CI)	(20–98)	(34–93)	(55–121)			
Total No of men	356	920	860	2688	4824	
			Ages 45–64 at entry			
Attack rate						
In 0–4 years follow up *						
Cases	11	54	52	141	158	
Rates	*3·3*	*6·5*	*6 9*	*8 0*	*7 1*	<0·01
RR%	41	81	85	100		
(95% CI)	(22–76)	(56–119)	(63–116)			
In over 4 years follow up:*						
Cases	7	26	59	124	216	
Rates	*1 5*	*3 5*	*4 5*	*5·0*	*4·3*	<0 001
RR %	29	69	89	100		
(95% CI)	(13–63)	(45–107)	(64–123)			

*Mortality in groups 1–4 ranges from 1 9 to 3 7 per 1000 man-years at 0–4 years of follow up and from 0 9 to 3 8 at over 4 years.

TOTALS OF PHYSICAL ACTIVITY IN LEISURE TIME

We examined the possibility that high overall physical activity in leisure time, as such, would be protective against the heart disease. We did this by estimating the total physical activity in all the forms previously described but after excluding vigorous aerobic exercise. Energy expenditures were calculated in a similar way to the figures used in studies of the American men.[9] The results after controlling for age were: for totals of < 2000 kcal/week, 213 cases and a coronary attack rate of 5·7; for 2000–2999 kcal/week, 113 cases and a rate of 5·2; for $\geqslant$ 3000 kcal/week, 148 cases and a rate of 5·3/1000 man-years. So for these data there was no gradient in coronary heart disease associated with total profiles of energy expenditure.

In group 4 coronary rates did not fall with increasing energy output. On the contrary: at energy expenditures of < 2000 kcal/week the attack rate was 5·9; at 2000–2999 it was 6·5; and at $\geqslant$ 3000 it was 7·0/1000 man-years. It may be added that group 4 rates were not affected by report of playing vigorous sports before entry in 1976.

EXERCISERS AND OTHER MEN

Table 5 examines the effect of selection for vigorous aerobic exercise in this homogeneous cohort, and some potential confounding factors, such as (A) family history and stature predispositions with plausibly a substantial genetic component; (B) expressed beliefs, attitudes, and health consciousness; (C) other health related behaviour; and (D) precursors of clinical coronary heart disease which may produce some circular double counting because of all the factors these are most likely also to be influenced by the effects of exercise.

It seems that those men taking vigorous aerobic exercise were at advantage in terms of coronary risk. For example, men in group 1 were less likely to have a family history of coronary heart disease and were more likely to have never smoked; and men in groups 1 and 2 were more likely to report a health conscious diet. The figures for totals of other physical activity in groups 1 and 2 may be pointing to a high overall energy output (with its attendant high intake) as a personality trait of vigorous exercisers.[20 21] It is instructive too that men in group 4, reporting none of the specific protective exercise, are particularly disadvantaged in terms of smoking, diet, weight gain (behavioural skills of today?), and in confidence about the possibility of personal control of future health—a marker for motives and the drive to exercise.[22 23]

Table 5 Relative frequencies of some possible selective factors for vigorous aerobic exercise (VAE) in male executive grade civil servants

Personal characteristic*	Vigorous aerobic exercise Group 1 (frequent/intense) (n = 216)† (%)	Group 2 (next lesser degree) (n = 424) (%)	Group 3 (residual, little) (n = 519) (%)	Group 4 (none) (n = 1185) (%)
(A)				
Family history				
Parent(s) died prematurely CVD‡	13	20	20	19
Stature:				
$\geqslant$5 ft 11 inch (1·80 m)	31	29	27	24
$\leqslant$5 ft 6 inch (1·68 m)	14	15	15	17
Energy output:§				
$\geqslant$3000 kcal	47	46	38	23
<2000 kcal	33	27	32	55
(B)				
"Believes can do anything to prevent ill-health in the future"	69	71	62	53
"Takes sufficient care of health"	43	32	27	28
"Takes enough exercise to keep healthy"	68	56	45	38
(C)				
Cigarette smoking:				
Never	40	27	25	23
$\geqslant$20 per day	11	12	16	21
Health conscious diet:¶				
3 or 4 points	29	30	18	16
No points	17	14	25	30
Weight in past year:**				
Stable	82	78	80	75
Gaining	8·1	7·8	8·0	12
Losing	9·4	14	12	12
(D)				
Body mass index:††				
$\leqslant$24	44	42	39	32
$\geqslant$27	10	14	18	24
Cardiovascular history:				
High blood pressure	4·1	5·9	8·0	9·6
Diabetes	1·1	1·2	2·3	1·8
Questionnaire angina‡‡	1·9	3·4	3·4	3·1
"Subclinical" CVD§§	6·5	9·6	12	13

Relative frequencies per cent, age-standardised by direct method. Men aged 45–64.
*All information reported at entry.
†n = 25% random sample of population.
‡F before 65, M before 70.
§Leisure time activity in week, excluding vigorous aerobic exercise.
¶1 point each for fruit, brown bread, no butter "usually every day"; 2 points for brown bread exclusively.
**"Stable" $\leqslant$ ±3 lb ("gaining" and "losing" >3 lb).
††kg/m^2.
‡‡Positive on LSHTM angina questionnaire.[34]
§§History of high blood pressure, and/or diabetes, and/or positive on angina questionnaire.
CVD, cardiovascular disease.

Table 4 also shows that the main observation is at least as strong in the later years, up to 9·3, as in the earlier years of follow up, partially refuting an explanation by secondary selection: that is, that men who were taking less exercise at entry already had limiting subclinical (heart) disease.

MULTIPLE FACTORS OF CORONARY HEART DISEASE

Table 6 shows the reported exercise groups, controlled for age and the main variables examined in table 5. In general, the gradients of the heart disease with standard risk factors are much as would be expected: compare the rates in men with a bad family history and a good family history; in short men and tall men; in smokers and non-smokers. Trends over the exercise groups, however, are similar to those of table 4—whether or not the men are at an advantage in terms of other factors, with good family history or bad, tall or short, and so on—lower coronary rates are evident in group 1 and to a lesser extent in group 2.

Multivariate analysis. Table 7 simultaneously "standardises" the exercise groups in each of the age bands for two, then three, then five of the other factors in a further attempt to allow for confounding of the main observation. This successive computation made little difference, however, to the overall picture of table 4—that is, the advantages of group 1 and of the older men in group 2 persisted—though the confidence intervals were widened. This emphasises the "independence" of vigorous aerobic exercise from classic risk factors.

ALL CAUSES DEATH RATE

Finally, it is necessary to know whether the reduction in coronary deaths was offset by deaths certified as other causes. This could arise from diagnostic and certification practices and/or excess deaths produced by vigorous aerobic exercise. There is no sign of this.

All deaths during the follow up were allotted to the four groups. Of the entrants aged 45–54, 3·1% (139 deaths) died in 1976–86 from causes other than coronary disease, as did 5·6% (278 deaths) of the entrants of 55–64. The risk of such death in the whole cohort of 45–64, standardised for age at entry and for cigarette smoking, was 3·1% in group 1 compared with 4·9% in group 4, the men reporting no vigorous aerobic exercise. For those men aged 55–64 the rate for smokers in group 2 was 8·7 compared with 9·0 in group 4 and for non-smokers it was 4·4 and 5·4 respectively. When non-coronary deaths were added to those from coronary heart disease, total death rates over the 9+ years of follow up were lower in men with an exercise related reduction in coronary heart disease, and their survival through middle age and into old age greater than in other men. Detailed analysis

Table 6 Vigorous aerobic exercise and other risk factors: attack rate from coronary heart disease (1976–86) in male executive grade civil servants (rates per 1000 man-years)

	*Vigorous aerobic exercise**							
	Group 1 (frequent/intense)		*Group 2 (next lesser degree)*		*Group 3 (residual, little)*		*Group 4 (none)*	
*Risk factors**	*Cases*	*Rates*	*Cases*	*Rates*	*Cases*	*Rates*	*Cases*	*Rates*
				Attack rate ages 45–64				
Family history:								
Parent(s) alive	14	*2·0*	44	*4·2*	94	*5·1*	198	*5·7*
Parent(s) died CVD	4	*(3·6)*	18	*6·8*	28	*6·5*	74	*8·8*
Stature:								
≥5 ft 11 inch (1·80 m)	3	*(1·1)*	15	*4·2*	29	*4·7*	52	*4·9*
5 ft 9 inch–5 ft 10 inch (1·75–1·78 m)	6	*2·6*	16	*4·2*	30	*4·7*	74	*6·0*
5 ft 7 inch–5 ft 8 inch (1·70–1·73 m)	5	*2·2*	18	*5·0*	41	*6·5*	89	*6·9*
≤5 ft 6 inch (1·68 m)	4	*(4·0)*	13	*6·4*	22	*6·7*	56	*7·8*
"Can do anything to prevent ill-health in the future":								
Definitely	9	*1·5*	48	*4·9*	67	*4·8*	150	*5·9*
Perhaps/largely chance	9	*3·7*	14	*4·2*	55	*6·3*	135	*6·7*
Cigarette smoking:								
Never	7	*2·2*	11	*3·2*	27	*4·5*	55	*5·7*
Ex	6	*1·8*	26	*3·9*	48	*4·7*	88	*4·6*
Current	5	*2·8*	25	*8·3*	47	*7·1*	129	*8·7*
Body mass index:								
<24	7	*1·9*	19	*3·4*	40	*4·3*	75	*5·5*
24–26·9	9	*2·4*	35	*6·0*	54	*5·7*	119	*6·2*
≥27	1	*(1·3)*	8	*4·8*	27	*7·1*	75	*7·3*
"Subclinical" CVD:								
Negative	14	*1·8*	54	*4·5*	92	*4·5*	185	*4·9*
Positive	4	*(7·5)*	8	*6·7*	30	*11*	87	*15*

*See tables 4 and 5 for description of groups and definitions.

of mortality in general will have to be based on larger numbers and so a longer follow up.[25 26]

Discussion

There is considerable evidence that exercise protects the heart against ischaemic disease[7 27 28] and it is now a central feature of national preventive campaigns such as the British "Look After Your Heart!".

Men engaging in the exercise identified as protective manifestly were a selected group. But tables 6 and 7 are the latest in a long line of analyses suggesting that it is the activity itself that protects, and that "self-selection" is not an adequate explanation of observed effects.[3 4 28–32] If selection bias is still an issue it will have to be resolved by other approaches, through biological markers perhaps or, in theory, a large randomised trial. Knowledge of selective factors is critical for understanding aetiology and in health promotion, but the practical message seems clear. Because nearly 30% of our older men were in groups 1 or 2, more than a (hypothetical) athletic minority may already be benefiting from adequate aerobic exercise in some sections of society.

Our participants were probably more healthy and fit than average because they are a working population and because we excluded men with a clinical history of coronary heart disease; they were more active too than the national population of their age and social class (2).[11]

Activities other than vigorous aerobic exercise were not associated with benefit in coronary rates, nor did high totals of physical activity per se—whatever their other benefits undoubtedly are.[7] Incidentally, though the term "vigorous" is used, vigorous enough on average for a training effect in such men is intended, and in the totality of exercise "moderately intense" might be a more appropriate term. This is particularly the case for the older cohort of 55–64 in group 2 who were observed for mortality up to 73 years of age and who showed a benefit associated with a lesser degree of the identified vigorous aerobic exercise but again not with any other form of exercise. Because major anatomical and physiological determinants of oxygen transport and physical working capacity decline with age, less intense exercise of the appropriate kind may be adequate to induce and maintain cardiorespiratory training.[5–8 19 34] By the same token, the minority of American men who derive some protective benefit from even more moderate aerobic exercise (corresponding here to non-vigorous sports and ordinary "normal" walking) may have been less healthy, active, and fit on average than our participants, and thus more able to derive some benefit from less intense exercise. These are testable propositions.

In general, significant protection against the heart disease was seen in the British men with less frequent vigorous sports than the current consensus advises.[33] The duration of the episodes of sports and games could not be satisfactorily studied.

"HEAVY WORK"

In the previous study this was inconsistently and rather weakly associated with protection but now fuller and more representative data show no association at all. Unlike typical occupational heavy work, recreational heavy work is liable to be periodic (seasonal digging) or occasional (those heavy building jobs); the number of men reporting some such work was surprisingly large. The activity itself entails discontinuous lifting and carrying, pushing and pulling of heavy objects, and gripping against resistance by small muscles: and static loads with excessive rises in blood pressure may therefore occur.[7] This contrasts with the sustained, predominantly dynamic, rhythmic contraction of large skeletal muscles, as in swim-

Table 7 Vigorous aerobic exercise (VAE) and other risk factors: attack rates and deaths from coronary heart disease (1976–86) in male executive grade civil servants (rates per 1000 man-years) after multivariate analysis/standardisation[16]

	*Vigorous aerobic exercise**				
Standardisation	*Group 1 (frequent/intense)*	*Group 2 (next lesser degree)*	*Group 3 (residual, little)*	*Group 4 (none)*	*p*
	Ages 45–54 attack rate				
(I) For age, family history, and stature:					
Cases	10	38	77	125	
Rates	*2·2*	*6·3*	*6·1*	*6·5*	< 0·025
Relative risks (%)	35	98	95	100	
(95% CI)	(18–68)	(66–145)	(70–129)		
(II) For (I) plus cigarette smoking:					
Cases	10	38	77	125	
Rates	*2·4*	*6·3*	*6·3*	*6·3*	> 0·05
RR%	37	100	100	100	
(CI)	(19–74)	(66–149)	(73–137)		
(III) For (I) and (II) plus body mass index and "subclinical" CVD:					
Cases	10	38	76	124	
Rates	*2·2*	*7·8*	*6·5*	*5·9*	> 0·05
RR%	37	131	110	100	
(CI)	(18–77)	(81–211)	(77–158)		
	Ages 45–54 mortality				
(I) For age, family history, and stature					
Cases	3	20	34	52	
Rates	*(0·66)*	*3·3*	*2·7*	*2·6*	> 0·05
RR %	25	126	102	100	
(CI)	(8–81)	(73–216)	(65–159)		
(II) For (I) plus cigarette smoking:					
Cases	3	20	34	52	
Rates	*(0·63)*	*3·4*	*2·7*	*2·6*	> 0·05
RR %	24	132	106	100	
(CI)	(7–80)	(75–231)	(67–168)		
(III) For (I) and (II) plus body mass index and "subclinical" CVD:					
Cases	3	20	34	52	
Rates	*(0·58)*	*4·5*	*3·2*	*2·3*	>0·05
RR %	25	198	141		
(CI)	(7–93)	(103–378)	(83–240)		
	Ages 55–64 attack rate				
(I) For age, family history, and stature.					
Cases	8	24	45	146	
Rates	*2·4*	*3·4*	*4·5*	*5·9*	< 0·005
RR %	41	57	77	100	
(CI)	(20–87)	(36–90)	(54–110)		
(II) For (I) plus cigarette smoking:					
Cases	8	24	45	146	
Rates	*2·6*	*3·5*	*4·6*	*5·8*	< 0·005
RR %	44	60	78	100	
(CI)	(21–93)	(38–95)	(54–131)		
(III) For (I) and (II) plus body mass index and "subclinical" CVD:					
Cases	7	24	45	145	
Rates	*2·4*	*3·6*	*4·8*	*5·6*	< 0·025
RR %	43	64	86	100	
(CI)	(19–101)	(39–108)	(56–131)		
	Ages 55–64 mortality				
(I) For age, family history, and stature:					
Cases	7	19	37	117	
Rates	*2·1*	*2·6*	*3·8*	*4·7*	< 0·005
RR %	46	56	80	100	
(CI)	(21–100)	(34–92)	(55–117)		
(II) For (I) plus cigarette smoking:					
Cases	7	19	37	117	
Rates	*2·2*	*2·8*	*3·8*	*4·6*	< 0·01
RR %	49	64	86	100	
(CI)	(22–108)	(36–102)	(55–123)		
(III) For (I) and (II) plus body mass index and "subclinical" CVD:					
Cases	6	19	37	116	
Rates	*2·3*	*2·6*	*3·9*	*4·4*	< 0·05
RR %	53	59	90	100	
(CI)	(21–132)	(34–105)	(57–144)		

*See Tables 4 and 5 for description of groups and definitions.

ming, walking, cycling, distance running, rowing, and the like, that was found to be protective; and such activities are more likely to be performed with greater intensity "for exercise". It is possible, too, that the static element in the heavy work reported cancels out such benefit that any vigorous dynamic element in the activity might confer.[35] Little is known of the energy costs and metabolic responses, long term haemodynamic function, training effects, and risk factor relations of major common physical activities in the real situations of everyday life.

MECHANISMS OF PROTECTION[4 7 27 28]

Exercise is viewed as a "general cause" of good health,[2] and there is indeed evidence that all major processes of coronary heart disease are moderated by it. But it is not yet possible to assign weights in this apparent overdetermination.

Classic risk factors such as cigarette smoking, hypertension, or the body mass index were usually lower with exercise (table 5); and at the same time exercise counteracts them in some or large measure (as here in smoking, or overweight, table 6). Atherosclerosis may be reduced by the improved lipid profile, glucose/insulin dynamics,[36–38] and the lower blood pressure.[7]

What is more interesting is that to be protective the exercise apparently has to be continuing and current: this suggests an effect on the acute phases of coronary heart disease—

for example, fresh coronary thrombosis leading to acute obstruction, myocardial ischaemia, and arrhythmia. There is growing evidence that exercise can counter thrombosis by inhibiting clotting processes and platelet aggregation.[7,39–42] In a national necropsy survey incidental major coronary obstruction was reported less often as the occupational physical activity of those who had died increased.[43] The electrical stability of the heart may be enhanced, raising the threshold for arrhythmia—for example, by lowering catecholamine concentrations.[44] The reduction in extrasystoles in men reporting vigorous aerobic exercise[45] and the original observation that "sudden death" was low in the physically active workers[1] may also be relevant.

It is encouraging (tables 4 and 7) that lower coronary rates are so evident in later middle and early old age.[2,4,26,27,39] After a lifetime's build up of the underlying atherosclerosis, protection against the acute precipitating phases of the heart disease is then the more realistic hope.

The protective exercise is that which trains for cardiorespiratory fitness; this is conventionally assessed by the maximal oxygen uptake.[7,8,33,34] An hypothesis in terms of "fitness" offers another explanation of the requirement for the exercise to be continuing. As shown in training/detraining experiments,[46,47] fitness achieved by exercise cannot be stored. Studies have favourably if variably related cardiorespiratory fitness to classic risk factors and to the heart disease.[48–55]

We may conjecture further. Stamina or endurance—the capacity for sustained aerobic exercise using a high proportion of the maximal oxygen uptake—whatever its level—is far more responsive to aerobic training than the actual maximum itself.[56–58] Perhaps endurance fitness protects against coronary heart disease? Perhaps a reduction in the endurance fitness of the population is one of the consequences of the modern decline in physical activity, specifically of adequate aerobic exercise? An hypothesis in terms of endurance fitness would direct attention also to the optimal performance and adaptability, with training, of the heart itself—exemplified in the slower rate and increased stroke volume with given demands, and the greater electrical stability, myocardial perfusion, and, possibly, wall thickness.[7,8,34,47,59–62] Such a proposition also underlines the need for practical non-invasive methods of assessing endurance fitness and training in the population[63] and is yet another plea for physiology and epidemiology to get together.

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Appendix

STATISTICAL METHODS

The data were analysed by relating the number of observed cases to the man-years denominators, which were calculated as follows. For men counted as *cases*, the observation time was taken as the time from entry into the study until the date of occurrence of the event. For those who were not counted as cases, the observation time was terminated either at the end of the follow up period (30 April 1986) or at death from another cause. The total man-years observation was estimated by multiplying the total observation time for *non-cases* by four (it was a 25% sample) and adding to this the total observation time for all cases. Partition of man-years observation between cells of tables followed established practice.

Inclusion, as cases, of men aged >60 who had non-fatal first events would have introduced a serious possibility of bias because of the incomplete follow up of morbidity after retirement. This was avoided by adopting a different case definition for men below the age of 60. In men aged up to age 60, an attack was defined as a first recognised occurrence of clinical disease, whether fatal or non-fatal. After that age attacks are defined as coronary deaths. While this definition leads to a rather strange relation between attack rate and age, the statistical method we used requires only that the *effects* of variables of interest upon the attack rate are approximately the same for different age groups. Counts of attacks and corresponding man-years observation were tabulated in the age bands 45–54, 55–59, 60–64, and 65+, and standardised relative risk estimates, pooled over age, were calculated by Poisson modelling.[16]

Where standardised *rates* are shown, these were calculated by applying the fitted age specific rates for subgroups to the distribution of man-years observation by age for the entire cohort.

The validity of these assumptions was checked in two ways. Firstly, we examined the stability of relative risks by age and by stage of follow up; some of these analyses are reported in table 4. Second, all analyses were repeated (*a*) for first clinical episodes up to age 60 and (*b*) for mortality up to age 73. Although based upon many fewer cases, there was no suggestion that these analyses differed from the results of the composite analysis of all attacks as defined above. For analyses of *mortality* rates, the man-years observations were slightly greater than for attack rates. These have not been shown (since the discrepancy is negligible) but were used in the formal analyses.

The standard errors of the relative risk estimates obtained by Poisson modelling are rather optimistic, since no allowance is made for the fact that the man-years denominators were estimated from a sample of the cohort. Theoretical expressions for correct standard errors have been obtained only (*a*) for logistic regression analysis of the probability of disease occurrence at any time during follow up and (*b*) for individually matched analyses comparing each case with the corresponding "at risk" members of the sample cohort.[15] The former is straightforward but the latter requires special software, which was not available at the time. Here an approximate approach was adopted; the standard errors obtained for Poisson modelling were inflated by the same factor as if simple logistic regression had been used. Similar corrections were applied to the significance tests.

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ORIGINAL ARTICLES

Early detection of acute myocardial infarction: additional diagnostic information from serum concentrations of myoglobin in patients without ST elevation

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Abstract

The value of the 12 lead electrocardiogram, serum total creatine kinase, creatine kinase MB isoenzyme, and myoglobin for the early detection of infarction was evaluated within one hour of admission to the coronary care unit in 82 consecutive patients with suspected myocardial infarction. The 51 patients in whom infarction was diagnosed during the first 24 hours after admission had a higher prevalence of ST elevation (64% *v* 11%), higher median serum myoglobin (136 µg/l *v* 34 µg/l), higher serum creatine kinase (77 IU/l *v* 34 IU/l), and higher MB isoenzyme (7 IU/l *v* 4 IU/l) than those in whom it was not. Stepwise logistic regression analysis in 70 patients in whom the electrocardiogram and serum myoglobin were suitable for analysis showed that serum myoglobin was the variable most closely associated with infarction, and contributed additional diagnostic information when ST elevation was entered into the model first. Serum myoglobin remained associated with myocardial infarction when patients who had had symptoms for < six hours were analysed. An algorithm based on a rapid agglutination test for myoglobin and ST elevation on the electrocardiogram gave an accurate diagnosis in 82% of patients. This approach gave early and rapid recognition of acute myocardial infarction and warrants further examination.

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Early detection of acute myocardial infarction to identify patients who are suitable for thrombolytic treatment usually includes electrocardiographic changes.[1-3] ST elevation on the electrocardiogram may, however, be absent in the early phase in up to 40% of patients.[4-7] Release of serum markers of myocardial necrosis, such as creatine kinase MB and myoglobin, may help to identify patients with infarction,[8] where thrombolytic treatment may reduce mortality.[9] This study sought to establish which markers of myocardial infarction could be used, in addition to the electrocardiogram, to diagnose correctly most patients.

Patients and methods

PATIENTS

Consecutive patients presenting to an emergency department were seen by a physician on duty who made a clinical diagnosis of suspected acute myocardial infarction requiring admission to the coronary care unit. Eighty two patients met the following inclusion criteria: (*a*) cardiac chest pain unrelieved by sublingual glyceryl trinitrate or nifedipine, (*b*) chest pain lasting >1 h but <24; (*c*) age $\leqslant 65$ years. We excluded all patients with shock (systolic blood pressure <90 mm Hg with clinical evidence of hypoperfusion), patients with recent trauma including cardiopulmonary resuscitation, and patients with known severe renal, muscular, or infectious disease. All patients had a 12 lead electrocardiogram recorded and a 10 ml blood sample obtained within one hour of admission to the coronary care unit. A positive diagnosis of myocardial infarction was based on the World Health Organisation criteria. The mean delay from arrival at hospital and admission to the coronary care unit was 108 minutes (range 10–400).

ELECTROCARDIOGRAM ANALYSIS

The electrocardiogram was read by two independent observers, who were unaware of the clinical details. The observers classified the electrocardiograms into three groups: type 1—ST elevation >1 mm in a limb lead or 2 mm in two precordial leads, irrespective of the presence of Q waves; type 2—any electrocardiographic abnormality, including right or left bundle branch block, ST depression, T wave inversion, or ST elevation less than the criteria for type 1 electrocardiogram; type 3—normal electrocardiogram, including minor ST and T wave changes and isolated fascicular blocks.[6] Each electrocardiogram was assigned to a group according to the most severe abnormality (type 1 > type 2 > type 3) that was seen.

SERUM ANALYSIS

Ten millilitres of blood was withdrawn from an antecubital vein. The blood was centrifuged, then serum was taken off and divided into two. The serum was stored at $-20°C$ until assays were performed. Total creatine kinase and its MB isoenzyme were measured by an enzyme immunoinhibition assay kit (Boehringer-Mannheim Diagnostica). We measured serum myoglobin concentrations in batches of 20 samples by a radioimmunoassay, using a double antibody for myoglobin (NMS Pharmaceuticals, Inc)[10] and concurrently we also measured serum myoglobin by a rapid latex agglutination test (Boehringer Diagnostica). This test takes 10 minutes to perform and produces a semiquantitative analysis in the range 90–1600 μg/l.[11] Data were incomplete in 14 patients because serum samples were not large enough for myoglobin assay,[8] electrocardiographic tracings were poor[4] and serum samples were not available for creatine kinase analysis.[2]

DATA ANALYSIS

We calculated the median and 25th and 75th percentiles for the continuous variables and used the Wilcoxon rank sum test for between group comparisons and Fisher's exact test for analysis of diagnostic groups. The association between continuous variables was analysed by the Spearman rank correlation test. The relative importance and independent contribution of each variable for identifying the correct diagnosis was examined by stepwise logistic regression analysis. Values from serum myoglobin determined by radioimmunoassay were plotted as a cumulative distribution function for patients with and without myocardial infarction. This function gives the probability that the serum myoglobin is less than or equal to a particular value, and can therefore be used to identify a cut off for an abnormal test according to the sensitivity and specificity required. Statistical significance was taken as $p < 0{\cdot}05$.

Results

STUDY POPULATION

On follow up 51 patients were diagnosed as having an acute myocardial infarction. The remaining 31 patients were diagnosed as having unstable angina pectoris or non-cardiac chest pain. Table 1 shows the characteristics of the study population. Thirteen patients in the group with myocardial infarction and eight in the group without had chest pain lasting > 6 h.

ELECTROCARDIOGRAMS

There were 78 electrocardiograms suitable for analysis (table 2). The distribution of electrocardiographic abnormalities (type 1 and type 2) differed significantly between the group with myocardial infarction and the group without (Fisher's exact test, $p < 0{\cdot}001$).

Table 1 Data on study population (medians with interquartile range for continuous variables in parentheses)

Variable	*MI (n=51)*	*Non-MI (n=31)*	*p*
Male sex	41 (80%)	27 (87%)	0·55
Age (years)	56 (49–60)	55 (51–57)	0 27
Chest pain (h)	4 (2–7)	3 (2–9)	0·90
Total CK (IU/l)*	77 (11–175)	34 (22–47)	0·0001
CK-MB (IU/l)*	7 (3–19)	4 (3–6)	0·02
Myoglobin (μg/l)†	136 (76–335)	34 (22–42)	0 0001

CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; MI, myocardial infarction

*Data not available on one patient with myocardial infarction and one without.

†Data not available on five patients with myocardial infarction and three without.

Table 2 Classification of admission electrocardiogram

ECG criteria	*MI n=50(%)*	*Non-MI n=28(%)*	*Total n=78(%)*
Type 1 (ST elevation)	32 (64)	3 (11)	35 (45)
Type 2 (abnormal)	15 (30)	21 (75)	36 (46)
Type 3 (normal)	3 (6)	4 (14)	7 (9)

Electrocardiograms were analysed by two observers who were unaware of the clinical data and classified as described in Methods section. The data are shown as number of patients with each type of electrocardiogram. Electrocardiograms were not suitable for analysis in one patient with myocardial infarction and in three without. See footnote to table 1 for abbreviations

CREATINE KINASE AND MB ISOENZYME

Serum concentrations of total creatine kinase and its MB isoenzyme were measured in 80 patients and both were significantly higher in the group with myocardial infarction during admission than in the group without (table 1). There was a significant positive correlation between the total creatine kinase and its MB isoenzyme in the group with myocardial infarction ($r = 0{\cdot}85$; $p < 0{\cdot}0001$). In those with myocardial infarction the duration of chest pain was positively correlated with serum concentrations of both total creatine kinase and its MB isoenzyme ($r = 0{\cdot}34$, $p < 0{\cdot}02$; $r = 0{\cdot}31$, $p < 0{\cdot}03$ respectively). No such relation was seen in the group without myocardial infarction (creatine kinase, $r = 0{\cdot}15$; creatine kinase MB, $r = 0{\cdot}13$). When patients with chest pain lasting more than six hours were excluded from the analysis, there was no relation between concentrations of creatine kinase or its MB isoenzyme and the duration of chest pain ($r = 0{\cdot}20$ and $r = 0{\cdot}17$ respectively).

MYOGLOBIN

Serum myoglobin was measured in 74 patients. The concentration of serum myoglobin was significantly higher in the group with myocardial infarction than in the group without (table 1). There was no appreciable correlation between the duration of symptoms and the serum concentration of myoglobin in either of the groups ($r = 0{\cdot}18$ in those with myocardial infarction and $r = 0{\cdot}13$ in those without). Serum myoglobin was also analysed by the rapid latex agglutination semiquantiative kit. There was a strong association between the two analyses ($\chi^2 = 49{\cdot}44$, $p < 0{\cdot}0001$). The kit was positive (concentration > 90 μg/l) in 57% of

Table 3 Semiquantitative analysis of serum myoglobin

Kit reading	*MI n=46(%)*	*Non-MI n=28(%)*	*Total n=74(%)*
1 (< 90 μg/l)	20 (43)	27 (96)	47 (64)
2 (90–200 μg/l)	9 (20)	0 (0)	9 (12)
3 (200–400 μg/l)	16 (35)	1 (4)	17 (23)
4 (400—1600 μg/l)	1 (2)	0 (0)	1 (1)

Serum myoglobin was measured by a rapid latex agglutination test. The semiquantitative analysis was obtained by diluting original serum sample serially if the initial reading was positive. Each step was read after five minutes. The data are shown as number of patients in each range. Samples were too small for analysis in five patients with myocardial infarction and three without. See footnote to table 1 for abbreviations.

Table 4 Univariate association with myocardial infarction

Variable	*All patients (n = 68)*	*Chest pain < 6 hours (n = 49)*
Myoglobin	28·66	23·74
Myoglobin by kit	16·95	15·11
ECG class 1	15·04	11·55
ECG class 2	9·53	5·07
Total CK	6·31	3·09
CK-MB	4·57	1·86

Univariate association with myocardial infarction as measured by logistic regression analysis. The data include only patients in whom all variables were measured. Table entries are χ^2 statistics with one degree of freedom. When χ^2 is > 3·84, p < 0·05. See footnote to table 1 for abbreviations.

patients with myocardial infarction and negative in 96% of patients without myocardial infarction (p < 0·0001). Table 3 shows the results of the semiquantiative analysis of serum myoglobin.

LOGISTIC REGRESSION ANALYSIS

The variables that might have been associated with myocardial infarction were analysed by stepwise logistic regression analysis in the patients in whom all variables were measured—both in the total group (n = 68) and those with chest pain lasting < 6 h (n = 49). Table 4 lists these variables. Serum myoglobin was the strongest individual predictor of myocardial infarction (χ^2 = 33·49; p < 0·0001). After adjusting for the association between presence of ST elevation and myocardial infarction (χ^2 = 18·11), inclusion of the myoglobin concentration doubled the diagnostic information (χ^2 = 20·39, p = 0·0001). Similar information was obtained when the myoglobin kit was analysed according to the same model (table 5). In a secondary analysis, the association between the same variables was examined after excluding 21 patients with chest pain lasting > 6 h. The serum concentration of myoglobin remained a good test for the diagnosis of myocardial infarction (χ^2 = 26·34, p < 0·0001). Presence of ST elevation did not yield significant additional information in this model.

Discussion

Most trials of intravenous thrombolytic agents have used ST elevation on the electrocardiogram as an inclusion criterion. The recently published data from the ISIS-2 trial found a reduced mortality in patients with and without ST elevation.[9] Since the induction of a fibrinolytic state is associated with increased morbidity, additional testing would be useful in the early identification of patients with acute myocardial infarction.

Table 5 Multivariate contribution of myoglobin and electrocardiogram to diagnosis of myocardial infarction

Variable	*Alone*	*Added contribution*
ECG (ST elevation)	18·11	5·01
Myoglobin concentration (radioimmunoassay)	33·49	20·39
ECG (ST elevation)	18·11	13·52
Myoglobin kit	19·60	15·01

Table entries are χ^2 statistics with one degree of freedom, based on logistic regression analysis. When χ^2 is > 3·84, p < 0·05. "Added contribution" described the extent to which one variable contributes any diagnostic information after adjustment for the other variable. The model only includes the patients for whom both the electrocardiogram and serum myoglobin were available for analysis (n = 70).

In accordance with previous studies[4–7] we found ST elevation to be the most sensitive electrocardiographic criterion. The proportion of patients presenting with ST elevation during myocardial infarction varies from 18%[12] to 81%[4] (mean 61%). In our series, ST elevation correctly identified 64% of patients with myocardial infarction (11% false positive rate) (table 2). But on the criterion of ST elevation 36% of patients would not have been eligible for thrombolytic treatment. In our series, only 6% of patients with myocardial infarction had a "normal" electrocardiogram. Eleven per cent of patients without myocardial infarction had ST elevation. We do not know why this was. But others reported that the probability of myocardial infarction was low in the presence of ST elevation when there was a past history of myocardial infarction.[13] We could not corroborate this finding in our series.

Raised serum concentrations of total creatine kinase and its MB fraction, though very sensitive and specific, tend to occur later than ST segment changes during the course of myocardial infarction. Our data indirectly support this finding because we found a significant positive correlation between the duration of chest pain and the serum concentration of creatine kinase and its MB isoenzyme. This relation disappeared when we analysed patients who had had chest pain for < 6 h. Furthermore, both creatine kinase and the MB isoenzyme were independently associated with myocardial infarction in the total study population, but this relation was not apparent when patients with prolonged chest pain were excluded.

Several studies have compared creatine kinase and creatine kinase MB with myoglobin during the early phase of myocardial infarction. In general these studies have found that serum myoglobin has a higher diagnostic sensitivity than creatine kinase and its isoenzyme,[8 14] though one study found no difference between the early rise of creatine kinase MB and myoglobin.[15] Our data support the superiority of myoglobin as an early marker of myocardial infarction because we found that myoglobin was a strong independent predictor of myocardial infarction in patients with symptoms of short duration.

Serum concentrations of myoglobin above the normal range have been found as early as one hour after myocardial infarction, with peak activity in the range of 4–12 hours.[16] In addition, it has been suggested that serum myoglobin mirrors the early course of myocardial necrosis; this was substantiated by the temporal relation between myoglobin release and electrocardiographic changes in infarction.[17] The overall cumulative release of myoglobin also correlates well with infarct size. Despite these impressive characteristics, serum myoglobin has not been used extensively for routine analysis in myocardial infarction. The main reason has been the very long assay times

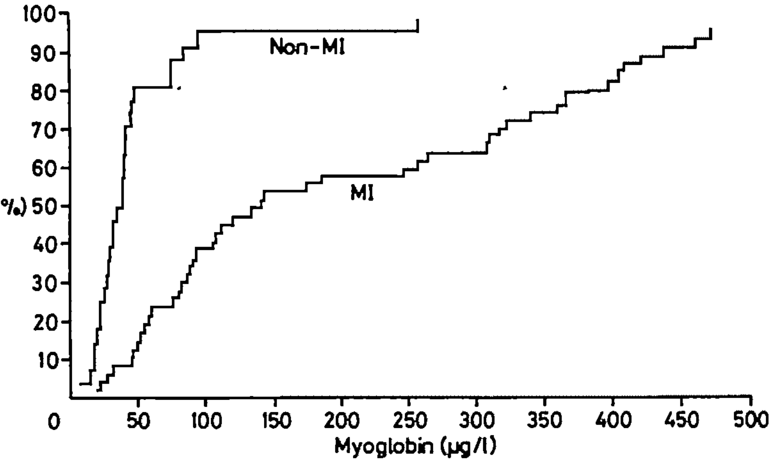


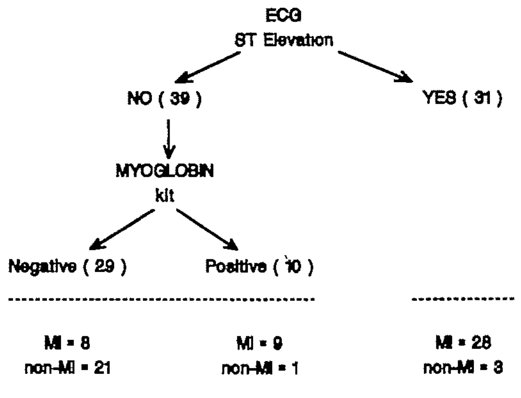
Figure 1 Cumulative distribution function describing the percentage of patients (ordinate) with and without a diagnosis of myocardial infarction for a given serum concentration of myoglobin (abscissa), as analysed by the radioimmunoassay. For example, the concentration was < 50 μg/l in 80% of those without myocardial infarction and in 13% of the patients with myocardial infarction. MI, myocardial infarction.

required, though more recent assays are becoming shorter. The rapid latex agglutination kit for myoglobin gives a result within ten minutes and can be performed by the bedside.

We found a good correlation between the serum concentration of myoglobin as measured by both the radioimmunoassay and the rapid latex agglutination kit. Other investigators have described similar findings, but noted a low reproducibility in the 80–140 μg/l range.[18] The diagnostic information was greater with the serum test for myoglobin than with the kit method. The results of the radioimmunoassay showed that many patients with myocardial infarction had serum concentrations in the range of 50–90 μg/l (fig 1). Had 50 μg/l been used as the upper limit of normal, the sensitivity would have been 87% and the specificity 82% in this study population. This underscores the importance of establishing a normal range for the particular population under investigation so that suitable sensitivity and specificity can be developed.

The adjunctive value of serum concentrations of myoglobin to the electrocardiogram is clearly established in this study—the diagnostic accuracy of ST elevation was doubled. The electrocardiogram made only a small additional contribution to the diagnosis of myocardial infarction once the serum concentration of myoglobin was measured by radioimmunoassay. Similar findings were noted when the myoglobin kit was used. Valuable time would be lost if the radioimmunoassay was performed during myocardial infarction. The kit gives less diagnostic information than the radioimmunoassay but it still enhances the diagnostic accuracy. In particular, 50% of patients with initially negative electrocardiograms and myocardial infarction were correctly diagnosed on the basis of their serum myoglobin concentrations, without an increase in the percentage of false positive results (fig 2). So a stepwise approach could be used and might improve the rapid identification of patients with myocardial infarction.

Figure 2 Algorithm for diagnosis of myocardial infarction in patients in whom both the electrocardiogram and serum myoglobin were available for analysis (n = 70). The algorithm is based on the assumption that additional testing is only necessary in patients without ST elevation. The calculated sensitivity was 82% and the specificity was 84%. MI, myocardial infarction.



We examined potential markers of early myocardial infarction. In 82 consecutive patients ST elevation on the electrocardiogram and serum myoglobin were the variables that best identified myocardial infarction. A short algorithm can be performed in ten minutes and gave an accurate diagnosis in 82% of patients. The hypothesis that rapid determination of serum myoglobin may improve the speed and accuracy of diagnosis in patients with suspected acute myocardial infarction deserves further evaluation.

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Importance of reciprocal ST segment depression in leads V5 and V6 as an indicator of disease of the left anterior descending coronary artery in acute inferior wall myocardial infarction

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Abstract

The purpose of this study was to determine the coronary angiographic correlations (specifically disease of the left anterior descending coronary artery) of reciprocal ST segment depression appearing during inferior acute myocardial infarction. Forty six patients (41 men and five women; mean age 56 years) were allocated into two groups based on the extent of precordial ST segment depression: widespread (V1–V6) ST depression *v* localised (V1–V4) ST depression. Patients with no reciprocal ST depression or patients with ST depression in V1–V4 but with ST elevation in V5 and V6 (inferolateral acute myocardial infarction) were excluded. All patients were catheterised during hospital admission for infarction. Twenty four of the 28 patients with ST depression in V1–V6 had significant lesions in the left anterior descending coronary artery whereas 16 of the 18 patients with ST depression in V1–V4 had insignificant or no lesions in the left anterior descending artery. The sensitivity, specificity, and positive and negative predictive values of widespread ST depression in predicting disease in the left anterior descending coronary artery were 92%, 80%, and 86% and 89% respectively.

In patients with inferior acute myocardial infarction and precordial ST depression, the extent of ST depression is of clinical significance. Widespread (V1–V6) ST depression suggests disease of the left anterior descending coronary artery, whereas localised ST depression (V1–V4) indicates its absence.

Inferior acute myocardial infarction in its early stages is usually accompanied by ST segment depression in the precordial leads. The clinical significance of this ST segment depression has been the subject of recent investigations because of the possibility that this reciprocal ST segment depression indicates additional anterior wall ischaemia.[1] Furthermore, it has been suggested that ST segment depression is an indicator of disease of the left anterior descending coronary artery.[2] In this study, we evaluated the frequency of disease in the left anterior descending artery in patients with inferior acute myocardial infarction in relation to the extent (widespread *v* localised) of precordial ST depression.

Patients and methods

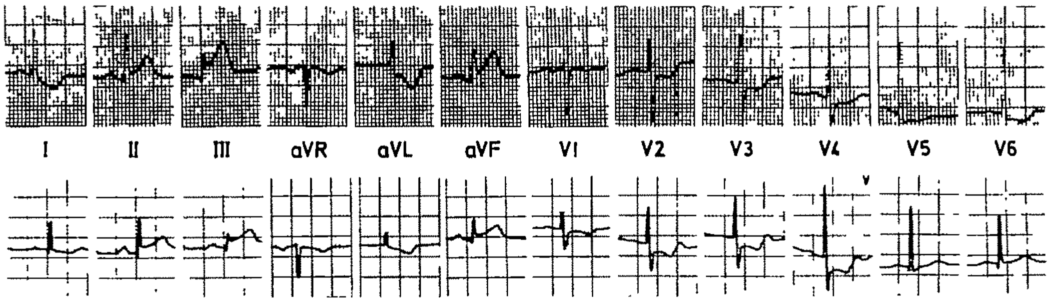
We reviewed the admission electrocardiogram of patients admitted to hospital with a first inferior acute myocardial infarction and without previous acute myocardial infarction at any other site who underwent coronary angiography during the same hospital admission.

PATIENTS

We studied 46 patients with inferior acute myocardial infarction. Thirty six of these patients came from our patient population who had had coronary angiography during the same hospital stay, usually for clinically indicated reasons (post-infarction angina, young age) during the years 1986–87. Ten additional patients were selected from a cohort of 100 patients admitted with acute myocardial infarction and treated with thrombolytic agents, who had cardiac catheterisation performed within the next 48 hours. The total group consisted of 41 men and five women aged 39–73 (mean 56 years).

SELECTION CRITERIA

The diagnosis of acute myocardial infarction was based on the classic triad of severe chest pain, evolving ST-T changes with development of abnormal Q waves, and an increase in the serum concentrations of cardiac enzymes. Patients were included if the admission electrocardiogram showed ST segment elevation of at least 1·5 mm in the inferior leads (usually leads III and aVF), and reciprocal ST segment depression defined as > 1 mm horizontal or downward sloping ST depression at 0·08 s from the J point of the QRS complex in the anteroseptal leads (usually V2 and V3). Patients with no ST segment depression in leads V1–V4 and/or patients with ST segment elevation (> 1 mm) in leads V5 and V6 (owing to lateral wall involvement) were excluded. The 46 patients included in the study were divided into two groups according to the extent of ST segment depression. The first group (28 patients) showed widespread ST segment depression (V1–V6) and the second



Examples of electrocardiograms in patients with inferior acute myocardial infarction showing widespread V1–V6 (top panel) and localised V1–V4 (bottom panel) reciprocal ST segment depression.

group (18 patients) showed ST depression only in V1 to V4 (isoelectric ST in V5 and V6) (figure).

Coronary angiography (by Judkins's or Sones's technique) was performed in all patients during the hospital admission for acute myocardial infarction. A significant coronary stenosis was defined as an obstruction of $\geq 70\%$ of the luminal diameter in one or more projections. The coronary anatomy was reviewed by two observers who had no prior knowledge of the patient's electrocardiogram. For the purpose of this study, disease of the left main coronary artery (obstruction $>50\%$) was regarded as disease of the left anterior descending coronary artery.

STATISTICAL ANALYSIS

We used χ^2 analysis (with Yates's correction) to determine whether the frequency of disease of the left anterior descending coronary artery was significantly different in the two electrocardiographic groups. In addition, we calculated the sensitivity, specificity, and positive and negative predictive value of widespread ST segment depression for disease of the left anterior descending coronary artery.

Results

Both groups were similar in terms of age, sex, and degree of ST depression in leads V1–V4. Of 28 patients with widespread ST segment depression (V1–V6) 24 (86%) had significant lesions of the left anterior descending coronary artery (two patients had disease of the left main coronary artery) whereas 16 (89%) of the 18 patients with ST segment depression in V1–V4 had insignificant or no disease of the left anterior descending coronary artery ($p < 0{\cdot}005$). The sensitivity, specificity, and positive and negative predictive value of the presence of widespread ST segment depression for the recognition of disease of the left anterior descending coronary artery were 92%, 80%, and 86% and 89% respectively.

Discussion

Much has been written about the significance and clinical implications of the presence or absence of ST segment depression in the precordial leads during inferior acute myocardial infarction. In general, it has been shown that precordial ST segment depression during inferior acute myocardial infarction indicates a larger infarction, predicting a worse prognosis, especially if the ST segment depression lasts for more than 48 hours.[3–6]

Though some studies showed that ST segment depression in patients with acute myocardial infarction indicates additional anterior wall ischaemia[1 2 7–10] others showed that ST depression represents a reciprocal phenomenon that may be distorted by concomitant right ventricular or lateral left ventricular involvement.[11–13]

In several studies the coronary anatomy (especially that of the left anterior descending coronary artery) was examined in patients with inferior acute myocardial infarction with reciprocal ST segment depression and in those without. The results of these studies were also contradictory. Gibson *et al* and Lew *et al* found no difference in the frequency and the extent of coronary artery disease and in the frequency of disease of the left anterior descending coronary artery between patients with inferior acute myocardial infarction with precordial ST depression and in those without.[5 6] In contrast, Gibelin *et al* found a significantly higher frequency of left coronary disease (left anterior descending and circumflex arteries) in patients with ST depression.[14] Similarly, Salcedo *et al* found a high frequency of disease of the left anterior descending coronary artery (96%) in patients with ST depression.[2] None of the eight patients without reciprocal precordial ST depression had disease of the left anterior descending coronary artery. Similar results were reported by Akhras *et al*.[10]

We studied the frequency of disease of the left anterior descending coronary artery in patients with inferior acute myocardial infarction and precordial ST depression. We divided them into two groups based on the extent of ST depression (V1–V6 *v* V1–V4 only). This division was arbitrary but was, however, based on our preliminary observations. We found that pure reciprocal changes are usually confined to the anteroseptal leads (V1–V4) whereas direct anterior subendocardial ischaemia is usually seen in the lateral leads (V4–V6).[15 16]

We found that 24 (86%) out of 28 patients with widespread ST depression had significant disease of the left anterior descending coronary artery, whereas only two (11%) out of 18 patients with localised ST depression (VI–V4) did ($p < 0{\cdot}005$). These results gave sensitivity, specificity, and positive and negative predictive values of 92%, 80%, 86% and 89% respectively.

Our results suggest that localised ST segment depression in V1–V4 is purely a reciprocal phenomenon, but that widespread ST depression (including V5 and V6) is a more complex phenomenon that probably indicates a reciprocal phenomenon and some additional ischaemic process unrelated to the acute occlusion of the artery, which is likely to be related to disease of the left anterior descending coronary artery. This additional ischaemic process is most probably subendocardial (represented by ST depression) and not necessarily severe enough to cause further haemodynamic embarrassment.

Our study had certain limitations. Firstly, we studied a specific subgroup of patients with inferior acute myocardial infarction. We included only patients with ST depression and patients without ST segment elevation in the lateral leads (V5 and V6); therefore we did not examine the implications of ST depression in V1–V4 in patients with inferolateral acute myocardial infarction. Secondly, since this is a retrospective study we cannot be certain that the precordial leads, especially V5 and V6, were properly positioned. If they were misplaced towards V4 the tracing could be misinterpreted as showing widespread ST depression. We excluded the only patient in whom there was a discrepancy between leads V5 and V6 (that is ST depression in V5 and none in V6).

In patients with inferior acute myocardial infarction and precordial ST depression the extent of precordial ST depression may be of clinical significance. Widespread (V1–V6) ST depression suggests multivessel disease (specifically of the left anterior descending coronary artery) whereas localised ST depression (V1–V4) indicates that there is no disease of the left anterior descending coronary artery.

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QT dispersion: an indication of arrhythmia risk in patients with long QT intervals

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Abstract

Homogeneity of recovery time protects against arrhythmias whereas dispersion of recovery time is arrhythmogenic. A single surface electrocardiographic QT interval gives no information on recovery time dispersion but the difference between the maximum and minimum body surface QT interval may be relevant. This hypothesis was tested by measuring the dispersion of the corrected QT interval (QTc) in 10 patients with an arrhythmogenic long QT interval (Romano Ward and Jervell and Lange-Nielsen syndromes or drug arrhythmogenicity) and in 14 patients without arrhythmias in whom the QT interval was prolonged by sotalol. QTc dispersion was significantly greater in the arrhythmogenic QT group than in the sotalol QT group.

In patients with prolonged QT intervals, QT dispersion distinguished between those with ventricular arrhythmias and those without. This supports the hypothesis that QT dispersion reflects spatial differences in myocardial recovery time. QT dispersion may be useful in the assessment of both arrhythmia risk and the efficacy of antiarrhythmic drugs.

The QT interval is one of the most controversial and least understood features of the surface electrocardiogram. Low T wave amplitude and U waves contribute to difficulties of QT measurement. The heart rate and the catecholamine dependence of the QT interval complicate the definition of normal values. None the less, the QT interval is clinically useful. Its prolongation has been related to an important arrhythmogenic risk in situations such as drug toxicity and in the Romano Ward and Jervell and Lange-Nielsen syndromes. Moreover, QT interval abnormalities identified high risk survivors of acute myocardial infarction.[1]

A single derived value of QT from an electrocardiogram embodies the concept of a global value for cardiac repolarisation time. Our previous work has shown that the QT interval varies from lead to lead of the surface electrocardiogram.[2] If such variation is merely a technical "artefact" caused, for example, by differences in unipolar versus bipolar leads, by differential tissue attenuation or by cancellation of vectors, then a derived average QT value from the electrocardiogram is scientifically valid.

But what if QT variation across the leads of the surface electrocardiogram reflects regional differences in repolarisation? The electrocardiogram does provide regional information about infarction and ischaemia. If the spread of QT values represents dispersion of repolarisation, this would be of great clinical importance. Increased dispersion is widely acknowledged to be an important basis for serious ventricular arrhythmias[3 4] and a decrease in dispersion probably explains the action of class III antiarrhythmic drugs.[5]

We have shown that regional differences in ventricular recovery time are expressed on the epicardial surface of the heart as reflected by monophasic action potentials measured during open heart surgery.[6] Linking this information with our observations on QT measurement from surface electrocardiogram leads,[2] we have now examined differences in the QT interval in the 12 lead electrocardiogram in two groups of patients with QT prolongation. In one group the QT prolongation was arrhythmogenic; all patients had confirmed arrhythmias caused by either the congenital long QT syndromes or by antiarrhythmic drug effects. In the other group, QT prolongation was caused by treatment with sotalol, a β blocker with class III effects; these patients had no arrhythmias.

Patients and methods

PATIENTS

We studied two groups of patients: an arrhythmogenic QT group and a group with QT prolongation caused by sotalol.

ARRHYTHMOGENIC QT

Ten patients with a history of ventricular arrhythmia and a long QT interval (nine congenital, one quinidine related) were identified either from published case reports (eight patients)[7–12] or from our own patient population (two patients). We considered nine other case reports but excluded them because the published electrocardiograms were not of adequate quality or did not show a timing reference. Selection was made before any measurement and no patient was rejected after initial selection.

SOTALOL QT

Fourteen patients were selected from a total of 41 who had received sotalol as part of a double blind randomised trial of oral sotalol one year

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Table 1 Characteristics of 10 patients with arrhythmogenic QT intervals

Patient	*Sex*	*Age (yr)*	*Diagnosis*	*Case source*
1	F	18	Romano Ward syndrome	Freeman Hospital patient
2	F	18	Romano Ward syndrome	Freeman Hospital patient
3	M	36	Romano Ward syndrome	Case 1 in reference 7
4	M	9	Romano Ward syndrome	Case 2 in reference 7
5	M	11	Romano Ward syndrome	Case 5 in reference 8
6	F	18	Romano Ward syndrome	Case 1 in reference 9
7	F	12	Jervell and Lange-Nielsen syndrome	Case 1 in reference 10
8	F	10	Jervell and Lange-Nielsen syndrome	Case 2 in reference 10
9	F	8	Jervell and Lange-Nielsen syndrome	Reference 11
10	M	50	Quinidine treatment for SVT	Reference 12

SVT, supraventricular tachycardia

Table 2 Electrocardiographic variables (maximum QTc, QT dispersion, QTc dispersion (ms)) and number of measurable leads in 10 patients with arrhythmogenic QT (history of ventricular arrhythmias) and 14 patients with long QT caused by sotalol treatment (no history of ventricular arrhythmias)

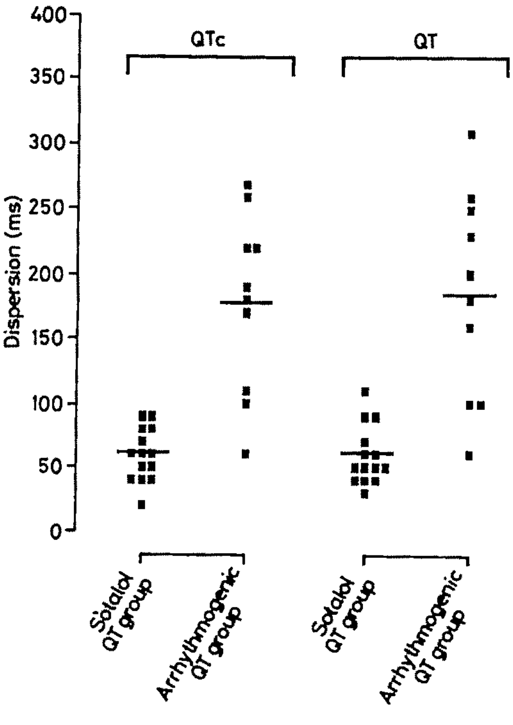
Electrocardiographic variable	*Arrhythmogenic QT group (n = 10)*	*Significance of difference (p)†*	*Sotalol QT group (n = 14)*
QTc max (range)	440–750	—	530–670
QTc max (mean (SE))	645 (32)	< 0·05	572 (10)
QTc dispersion (mean (SE))	178 (18)	< 0·0001	60 (7)
QT dispersion (mean (SE))*	185 (26)	< 0·0001	60 (7)
Number of leads measurable (range)	5–10	NS	4–10

*Difference between maximum and minimum QT (QTc). QTc max, maximum corrected QT interval †*t* tests performed on logarithmically transformed data.

after infarction.[13] They were all those who had a maximum corrected QT interval (QTc)[14] > 500 ms at one month. No patient treated with sotalol had symptomatic ventricular arrhythmias during one year follow up. All were in sinus rhythm. None had evidence of bundle branch block and none was taking drugs known to influence the QT interval, other than sotalol.

QT ANALYSIS

Standard 12 lead electrocardiograms were recorded in the arrhythmogenic QT group at either 25 or 50 mm/s, while those in the sotalol QT group were recorded at 50 mm/s. Electrocardiograms from the case reports were enlarged to an appropriate size for measurement. An observer used a digitiser (Calcomp 9000) to measure the QT intervals from the onset of the QRS to the end of the T wave, defined as a return to the T-P baseline. When U waves were present the QT was measured to the nadir of the curve between the T and U waves. Wherever possible, three consecutive cycles were measured in each of the 12 electrocardiogram leads and from the three values a mean QT and QTc was calculated. When the end of the T wave could not be reliably identified that lead was not included in subsequent analysis. QT dispersion was defined as the difference between the maximum and minimum QT occurring in any of the 12 electrocardiogram leads in which it could be reliably measured. QTc dispersion was also calculated.



QT and QTc dispersion in 10 patients with arrhythmogenic QT (history of ventricular arrhythmias) and 14 patients with long QT due to sotalol treatment (no history of ventricular arrhythmias).

STATISTICAL ANALYSIS

We used Student's unpaired *t* test to compare the group means and we calculated the confidence intervals.[15]

Results

Table 1 shows the age, sex, underlying diagnoses, and case source of the patients with arrhythmogenic QT intervals. Eight of the sotalol QT patients had suffered an anterior myocardial infarction and six an inferior infarction.

Table 2 shows the results of QT analysis. The number of measurable leads for the two groups was similar. For all three variables, QTc max, QT, and QTc dispersion, the standard deviations of the two patient groups increased with the means. To adjust for this, significance tests were performed on the data after logarithmic transformation. The QTc intervals were slightly longer in the arrhythmogenic QT group. Both QT dispersion and QTc dispersion were significantly greater in the arrhythmogenic QT group (95% confidence interval for the ratio of QTc geometric means was 2·01 to 4·3) (see figure). No patient in the sotalol group had a QTc dispersion > 100 ms while only one patient in the arrhymogenic group had a QTc dispersion < 100 ms.

Discussion

Our results of QT measurement in arrhythmogenic and non-arrhythmogenic patients support the concept that QT variability on the surface electrocardiogram is not a technical artefact but rather reflects regional myocardial electrical recovery. Our results challenge the concept of a single global value for the QT interval. Such a value has been reported to be clinically useful but usually only when markedly abnormal or when monitored for change. Our results suggest that much more information is available on the surface electrocardiogram regarding repolarisation than is reflected by a single QT value. But are the results reliable? The measurement methods have been painstakingly validated.[2] Surface electrocardiogram QT measurements can never be wholly accurate but we have previously shown that variation in interlead measurements far outweighs inaccuracies introduced by any other factor.

The maximum QTc was significantly greater in the arrhythmogenic group than in the sotalol group but there was considerable overlap between the groups. A QTc dispersion of 100 ms was better at separating the two groups than any single value of maximum QTc.

The concept that body surface QT variation reflects dispersion of repolarisation is supported by other work. Studies in patients with the long QT syndromes have shown large spatial differences in myocardial recovery time as shown both by the duration of monophasic action potentials in different parts of the ventricle[16] and by body surface mapping.[17] Moreover, bretylium, a class III as well as a class II antiarrhythmic agent, reduced temporal dispersion of effective refractory periods in dogs and this effect correlated with an increase in the ventricular fibrillation threshold.[5]

Our results do not prove that QT variability on the surface electrocardiogram reflects dispersion of repolarisation but they do support that hypothesis. The conventional 12 lead electrocardiogram remains in clinical practice more for historical than for scientific reasons. For the purpose of this research, different lead positions and consistent lead configurations (unipolar) have many attractions. We used the standard 12 lead electrocardiogram both because rare patient data (long QT syndromes) were available in this format and because, if the results of our study are accepted, a beguilingly simple and accessible clinical method could be used and tested by others. The proof of the concept must come from intraoperative studies in which epicardial monophasic action potentials are correlated with body surface electrocardiogram features. Such work is technically difficult but is in progress. Reliable, non-invasive access to dispersion of repolarisation could radically alter our approach to arrhythmias, our concepts and prediction of arrhythmogenesis, and the precision of prognosis.

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Changing role of non-invasive investigation in the preoperative assessment of congenital heart disease: a nine year experience

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Abstract

The total surgical experience of a supraregional paediatric cardiology unit over a nine year period (January 1980 to December 1988) was reviewed to assess the effect of the introduction of the full range of ultrasound techniques. A total of 1517 patients underwent cardiac surgery (955 cardiopulmonary bypass, 562 closed procedures). Of these, 485 patients (32%) did not undergo cardiac catheterisation before operation: 217 bypass (23% of all procedures under cardiopulmonary bypass) and 268 closed procedures (48%). The overall ratio of catheterisations to operations for patients undergoing palliative or corrective surgery fell from 0·97 (1980) to 0·38 (1988). The patients were classified as (*a*) neonates (0–28 days), (*b*) infants (one to 12 months), and (*c*) children (one to 14 years). The main impact of non-invasive surgical referral was in neonates (total catheter:operation ratio 0·38; neonates 0·2 for 1988). The surgical population was further divided according to the principal echocardiographic technique available: (*a*) 1980–4 cross sectional imaging; (*b*) 1985–6; imaging plus spectral Doppler ultrasound; (*c*) 1987–8; imaging plus spectral Doppler ultrasound and colour flow mapping. A fall in the catheter:operation ratio for all age groups was most pronounced in the last four years. This reflects increased familiarity and surgical confidence with non-invasive diagnostic assessment. The introduction of each new echocardiographic technique was associated with a significant fall in the total catheter:operation ratio compared with the preceding period. Six incorrect ultrasound diagnoses were made during the entire period; one of these patients died in the early postoperative period.

The integration of Doppler ultrasound with cross sectional imaging has made non-invasive assessment an increasingly practical alternative to preoperative cardiac catheterisation.

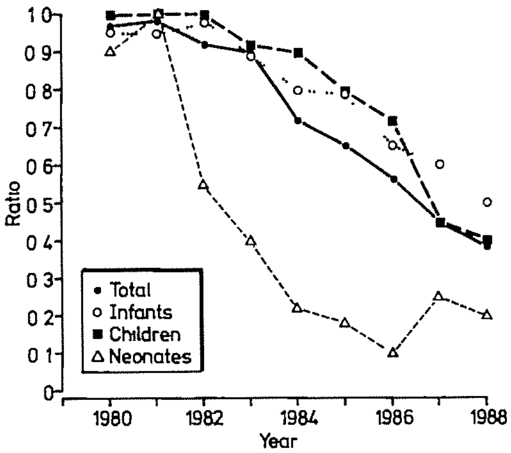
Cross sectional echocardiography has come to be accepted as an excellent non-invasive technique for morphological evaluation of congenital heart defects.[1 2] In young patients it provides detailed information about intracardiac structure, and with a sequential approach the precise connections, relations, and morphology can be evaluated in detail.[3] With the introduction of spectral Doppler and colour flow mapping it has become possible to derive haemodynamic information even in complex cardiac malformations.[4–6] The combined use of these techniques should provide much of the information previously only available from cardiac catheterisation and angiography.

Previous studies of non-invasive preoperative assessment in congenital heart disease have been restricted to small or selected groups of patients. There has not been a study of a total paediatric cardiology practice.[7–9] The Wessex region is one of the nine designated supraregional centres in England and Wales for neonatal and infant cardiac surgery. It serves a population of approximately 3·2 million people, and has a static annual number of livebirths of approximately 33 000. The population has remained virtually constant with little migration of the patient population out of or into the Wessex region. Virtually all infants or children with suspected congenital heart disease are referred to the regional centre. Some cases are referred from outside the region. A full range of paediatric surgical services except transplantation is available in the unit. Accurate statistics have been recorded for the Wessex region since 1980.

Cross sectional imaging has been available in the unit from 1980. Spectral Doppler scanning was introduced in 1984 and colour flow mapping in 1987. With each new introduction there has been a significant change in the unit's clinical practice, with increasing surgical referral on the basis of non-invasive investigations alone. We retrospectively analysed the impact of these changes on surgical referral patterns in paediatric heart disease.

Patients and methods

From January 1980 to December 1988, 1517 operations were performed on patients with various congenital heart defects. Initial assessment in all patients included clinical examination, relevant biochemical tests, chest *x* ray, electrocardiography, and echocardiography. Cross sectional echocardiography was carried out with ATL Mark III, Ultramark 4 (7·5 MHz, 5 MHz short and medium focus, or 3·5 MHz probes), or with Toshiba SSH



Graph showing the ratios of diagnostic cardiac catheterisations to operations for congenital heart disease from January 1980 to December 1988. The ratios are shown for the total surgical population and for the age group subsets (see text).

Table 2 Diagnoses in 189 neonates referred for operation without catheterisation

Diagnosis	*No*
DA	70
Coarctation/interrupted arch	47
Complex cyanotic CHD/shunt	29
Pulmonary stenosis	11
Truncus arteriosus	9
Pulmonary artery banding	5
Ventricular septal defect	5
Aortic stenosis	5
Transposition/anatomic repair	3
TAPVD	2
Atrioventricular septal defect	1
Miscellaneous	2

CHD, congenital heart disease; DA, ductus arteriosus; TAPVD, total anomalous pulmonary venous drainage.

60A or SSH 65A ultrasound systems (5 mHz, 3·7 mHz, or 2·5 mHz probes). Since 1984, duplex scanning with the Toshiba system and non-imaging continuous wave Doppler with the Vingmed SD 100 system were also used in evaluation. Colour flow mapping has been routinely used since 1987.

Surgical procedures in this period were divided into cardiopulmonary bypass and closed (non-bypass) procedures. The records of patients requiring diagnostic preoperative cardiac catheterisation were reviewed, and a ratio of diagnostic catheter procedures to operations was taken to represent patients requiring preoperative invasive assessment (figure). The patients were divided into three age groups: neonates (0–28 days); infants (one to 12 months), and children (one to 14 years). The cut off age of 14 years is the upper age limit for admission to the paediatric unit of the Wessex Cardiothoracic Centre. To define the influence of the echocardiography the patient population was further divided according to the principal non-invasive diagnostic technique(s) available: (*a*) 1980–4, cross sectional imaging alone; (*b*) 1985–6, cross sectional imaging plus pulsed and continuous wave Doppler; (*c*) 1987–8, cross sectional imaging with Doppler colour flow mapping. Although cross sectional echocardiography was available in 1980, the period 1980–81 was taken to represent a "learning period" with this technique because most patients also underwent diagnostic cardiac catheterisation during these two years.

Diagnostic errors (incomplete or incorrect diagnoses) in patients referred for surgery on ultrasound findings alone were identified. We attempted to define the influence of non-invasive and invasive assessment on the surgical outcome. We compared the proportion of patients undergoing diagnostic cardiac catheterisation in each period with that in the previous period using a χ^2 fourfold table with Yates's continuity correction.

Results

TOTAL POPULATION

As the routine use of cross sectional echocardiography increased there was a highly significant fall in the overall ratio of diagnostic catheterisations to operations (1980/81 *v* 1983/84; $p < 0{\cdot}001$). The subsequent introduction of pulsed and continuous wave Doppler and colour flow mapping also produced significant decreases in the ratio ($p < 0{\cdot}001$ and $p < 0{\cdot}025$ respectively) compared with the catheter:operation ratio for the preceding period (figure and table 1).

NEONATES

Of 284 operations performed on neonates over nine years (91 bypass, 193 closed), diagnostic cardiac catheterisation was required in 93 (33%) (51 bypass, 42 closed). Interventional catheterisation procedures for conditions that required later surgical correction (for example balloon septostomy for complete transposition) were classified as diagnostic cardiac catheterisation. The number of diagnostic catheterisation procedures continued to fall as confidence grew in the diagnosis of structural malformations by cross sectional echocardiography (catheter:operation ratio for 1980/81 *v* 1983/84, $p < 0{\cdot}001$). The addition of pulsed and continuous wave Doppler ultrasound to the routine preoperative assessment produced a further fall in preoperative diagnostic catheterisation

Table 1 Ratio of cardiac catheterisations to operations in all age groups (1980–88)

				Cardiopulmonary bypass			*Closed operations*		
Year	*Op total*	*Cath total*	*c:op*	*Op*	*Cath*	*c:op*	*Op*	*Cath*	*c:op*
1980	115	111	0·97	68	68	1·0	47	43	0·91
1981	131	129	0·98	82	82	1·0	49	47	0·96
1982	108	101	0·94	63	63	1·0	45	38	0·84
1983	166	141	0·9	108	106	0·98	58	35	0·6
1984	180	134	0·74	109	100	0·92	71	34	0·48
1985	167	107	0·64	98	79	0·81	69	28	0·41
1986	222	126	0·57	137	101	0·74	85	25	0·29
1987	233	108	0·46	157	74	0·47	76	34	0·45
1988	195	75	0·38	133	65	0·49	62	10	0·16
Total	1517	1032		955	738		562	294	

Cath, diagnostic cardiac catheterisations, Op, operations, c.op, ratio of diagnostic catheterisations to operations.

Table 3 Diagnoses in 119 infants referred for operation without catheterisation

Diagnosis	*No*
DA	33
Ventricular septal defect	16
Coarctation	14
Complex cyanotic CHD/shunt	13
Atrioventricular septal defect	9
Secundum atrial septal defect	8
Aortic stenosis	5
TAPVD	5
Pulmonary stenosis	3
Truncus arteriosus	3
Transposition/anatomical repair	2
Tetralogy of Fallot	1
Aortopulmonary window	1
Miscellaneous	6 (vascular ring, arteriovenous fistula etc)

See footnote to table 2 for abbreviations

Table 4 Diagnoses in 177 children referred for operation without catheterisation

Diagnosis	*No*
Secundum atrial septal defect	72
DA	37
Subaortic stenosis	11
Aortic stenosis/valvotomy	8
Ventricular septal defect	7
Coarctation	7
Tetralogy of Fallot	6
Atrioventricular septal defect	5
Aortic/pulmonary valve replacement	5
Aortopulmonary shunts	3
Pulmonary stenosis/valvotomy	3
PAPVD/TAPVD	2
Cor triatriatum	2
Miscellaneous	9

PAPVD, partial anomalous pulmonary venous drainage. See footnote to table 2 for other abbreviations.

(catheter:operation ratio for 1983/84 *v* 1985/86, $p < 0{\cdot}001$). The trend towards reduced catheterisation was especially pronounced in neonates requiring closed cardiac surgery. In 1987/88, 16/20 neonates undergoing shunt procedures, 15/15 patients with coarctation, and 16/16 neonates requiring duct ligation did not have preoperative catheterisation. This trend has been followed to a lesser degree for procedures requiring cardiopulmonary bypass. Table 2 categorises the individual diagnoses in those who had an operation without prior catheterisation.

INFANTS

Of 509 operations carried out in patients aged 1–12 months (328 bypass, 181 closed), 391 patients (274 bypass, 117 closed) required diagnostic cardiac catheterisation (total catheter:operation ratio 0·77) (figure). The ratio of diagnostic catheterisations to operation fell significantly with the introduction of each new non-invasive diagnostic technique (1980/81 *v* 1983/84, $p < 0{\cdot}005$; 1983/84 *v* 1985/86, $p < 0{\cdot}005$; 1985/86 *v* 1987/88, $p < 0{\cdot}05$). Separate analysis of the bypass and closed groups showed that the effect of cross sectional imaging alone was not statistically significant in either group. The introduction of spectral Doppler and colour flow mapping techniques, however, was associated with a significant decrease in preoperative catheterisation in infants undergoing surgical repair with cardiopulmonary bypass (1983/84 *v* 1985/86, $p < 0{\cdot}025$; 1985/86 *v* 1987/88, $p < 0{\cdot}005$). Table 3 lists the individual diagnoses for all infants undergoing surgery without prior catheterisation.

CHILDREN

Of 724 operations performed on children aged one to 14 years (536 bypass, 188 closed), diagnostic catheterisation was required in 548 patients (catheter:operation ratio 0·68) (figure). The catheter:operation ratio was similar for both bypass (0·77) and closed (0·72) procedures. Although the catheter:operation ratio decreased with the introduction of cross sectional imaging, the fall was not statistically significant for bypass or closed groups. The introduction of spectral Doppler and colour flow mapping, however, was associated with a significant fall in the catheter:operation ratio for the whole group compared with the preceding period ($p < 0{\cdot}001$).Table 4 lists the individual diagnoses for children referred to surgery without catheterisation.

DIAGNOSTIC ERRORS WITH ECHOCARDIOGRAPHY

There were six important incorrect ultrasound diagnoses in the nine years (0·01% of the number investigated non-invasively). One patient had multiple levels of coarctation. In a neonate with situs ambiguus, univentricular atrioventricular connection, and coarctation, the laterality of the aortic arch was misdiagnosed. In a patient with pulmonary atresia, ventricular septal defect, and bilateral arterial ducts, the absence of central pulmonary arteries was missed. In a fourth case, coarctation of the aorta was incorrectly diagnosed in a patient with a thrombosed descending aorta. In the fifth patient, despite apparent clinical and colour flow mapping evidence of a secundum atrial septal defect, no interatrial shunt was found at operation. Finally, in one patient with transposition of the great arteries and a ventricular septal defect, additional muscular ventricular septal defects were missed both by echocardiography and at the initial preoperative angiographic review. These were discovered on review of the angiogram in the immediate postoperative period. This patient underwent a Mustard procedure and had closure of a ventricular septal defect but died soon after operation.[10] Surgical mortality could not be directly attributed to errors in preoperative diagnosis in the remainder.

OPERATIVE MORTALITY

Operative or early mortality was defined as death occurring during the operation, within 30 days of operation, or during the period of hospital stay if this was longer than 30 postoperative days. During 1987 and 1988, when the surgical referral based on non-invasive diagnosis was at its highest, there were 11 (4%) early deaths among 245 patients referred for operation without cardiac catheterisation: neonates 7/69, infants 4/51, children 0/125. These figures compare favourably with the mortality figures for the same two year period for patients who underwent preoperative catheterisation: neonates 4/23, infants 6/65, and children 2/96.

The higher mortality for the neonates was not related to the primary diagnostic method (ultrasound or cardiac catheterisation) because the diagnosis in all 11 neonates who died was found to be complete and correct at operation. The individual diagnoses for the seven neonates who died after operation without cardiac catheterisation were: type I or type II common arterial trunk (three patients), coarctation with ventricular septal defect (two patients), pulmonary atresia with intact septum requiring pulmonary valvotomy and a shunt procedure (one patient), and cerebral arteriovenous fistula (one patient).

Discussion

Cross sectional echocardiography is a reliable method for identification of intracardiac morphology, and it can provide better information than cardiac catheterisation and angiography.[11] In most children extracardiac vascular structures can also be identified reliably.[12–14] With the current improvements in echocardiographic machines it is possible to categorise completely and systematically most congenital cardiac malformations. These echocardiographic findings have been extensively validated both at operation and necropsy and numerous studies have testified to the benefits of cross sectional echocardiography in the morphological assessment of congenital heart disease.

NEONATES AND INFANTS

In our experience cross sectional echocardiography had the biggest impact on the diagnostic assessment of sick neonates and infants. Cardiac catheterisation in this group is associated with considerable morbidity.[15,16] In most neonates with symptoms and an obstructive lesion of the outflow tract (for example critical aortic or pulmonary valve stenosis, coarctation of the aorta, or aortic arch interruption) operation can be based on morphology. For neonates with more complex malformations who require palliative procedures to regulate pulmonary blood flow (pulmonary artery banding or an aortopulmonary shunt) the surgical referral can be made on echocardiographic findings alone.[17] In 1987 and 1988, only 4/20 neonates who required an emergency shunt procedure and 1/5 who required pulmonary artery banding had prior catheterisation. They needed angiography for better definition of the size and distribution of the pulmonary vasculature.

Cross sectional imaging may be inadequate in several situations. Haemodynamic information such as the estimation of outflow tract gradients, valve regurgitation, or multiple sites of intracardiac shunting require additional techniques to assess blood flow. Pulsed and continuous wave Doppler echocardiography are complementary to cross sectional imaging in this assessment and have also aided identification of extracardiac abnormalities including coarctation of the aorta, interruption of the aortic arch, anomalous pulmonary venous drainage, or a ductus arteriosus.[18–20] It has become possible reliably to derive the pulmonary artery systolic presssure in a large proportion of patients from Doppler echocardiography by measuring the peak velocity of tricuspid regurgitation; for ventricular septal defects similar estimates can be made by measuring the velocity of the jet of the ventricular septal defect.[21,22]

The introduction of colour flow mapping in 1987 provided several additional advantages in diagnosis. In ventricular septal defects, colour flow mapping has proved more sensitive than angiography in the diagnosis of multiple defects.[23] With isolated defects, direct visualisation of the ventricular septal defect jet has enabled easier alignment of the jet for continuous wave Doppler interrogation. Colour flow mapping aided the assessment of valve regurgitation and helped in the recognition of extracardiac shunts such as patent ducts (25/25 neonates and infants had duct ligation without catheterisation in 1987/88), particularly in the sick preterm infant in whom the characteristic clinical signs are often absent and imaging alone is often unsatisfactory.[24] Pulmonary vascular structures are more easily identified in complex defects such as pulmonary atresia.[25] Other lesions for which corrective surgery is now being regularly performed without prior catheterisation include total anomalous pulmonary venous connection (7/7 patients in 1987/88), complete atrioventricular septal defect (7/10 patients), and common arterial trunk (10/11 patients).

The routine use of these techniques has therefore resulted in an important change in our clinical practice, shifting the emphasis from cardiac catheterisation and angiography towards ultrasound assessment. This is particularly true for palliative or corrective surgical procedures in the neonate that do not require cardiopulmonary bypass.

OLDER CHILDREN

Older children with simple lesions such as uncomplicated secundum atrial septal defect are referred for operation on the clinical and ultrasound findings alone. For 1987/88, 58/59 patients with secundum atrial septal defects were referred for operation without catheterisation. Similarly, all arterial ducts were ligated without additional investigation.

The relatively high catheterisation rate in the older children is related to several factors. In 1980 to 1984 after the introduction of cross sectional imaging, virtually every child who underwent surgery had preoperative cardiac catheterisation. First, this was the period during which physicians and surgeons assessed the value of the technique. It has been the policy of the paediatric cardiologists to measure the haemodynamic variables at catheterisation in most patients over the age of one year with moderate sized left to right shunts. Cardiac catheterisation was undertaken to measure the shunt and assess the pulmonary vascular resistance in 6/11 children who underwent closure of an isolated septal defect in 1987/88. Additionally, the relative values of echocardiography and cardiac catheterisation for the identification and characterisation of specific lesions were compared in several studies during this period; this accounted for some of the cardiac catheterisation procedures.[23,25] The catheterisation rate is also related to the problems inherent in the currently available methods for non-invasive diagnosis. With increasing age the available echocardiographic window may be reduced as the chest wall and lungs become bigger. Many of the older patients had also undergone palliative or corrective procedures at a younger age, with further reduction in echocardiographic visualisation because of acquired adhesions or implanted prosthetic material within the heart.[26] Thus in older patients with coarctation of the aorta suprasternal imaging often provides less satisfactory images of the arch. During this study, balloon angioplasty of coarctation was not undertaken and all patients with native coarctation or recoarctation underwent surgical repair. Preoperative cardiac catheterisation was performed in 12/14 children in 1987/88. For complex cyanotic heart disease requiring corrective surgery cardiac catheterisation was invariably required to assess the pulmonary vasculature and to calculate the pulmonary vascular resistance. All children undergoing a Fontan procedure, repair for tetralogy of Fallot, or correction of pulmonary atresia had cardiac catheterisation in the six months before operation.

In summary, the aim of any diagnostic technique is to provide the information necessary for correct management decisions. Although there has been a progressive fall in the ratio of diagnostic catheterisations to operations for all age groups over the nine years of review, this is the result of a combination of factors, and it is difficult to isolate the role of any individual diagnostic technique. Thus while significant falls in diagnostic catheterisation were associated with the introduction of pulsed/continuous wave Doppler and subsequently of colour flow mapping, the increasing experience with cross sectional echocardiography, improvements in image resolution, and the surgeons' confidence with the technique may all have contributed. Areas of inaccuracies with echocardiography, such as with multiple ventricular septal defects or complex pulmonary atresia, are also sometimes poorly defined by cardiac catheterisation and angiography. It is also reassuring that the avoidance of cardiac catheterisation did not significantly affect surgical mortality. On the basis of our experience, we conclude that with good quality imaging and Doppler echocardiography it is both feasible and safe to avoid cardiac catheterisation in selected patients with congenital heart disease. The growing acceptance of these techniques by surgeons is reflected in the increasing number of patients of all age groups undergoing cardiac operation on the basis of ultrasound findings alone.

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died we cannot be certain that a left pneumonectomy would have achieved a satisfactory long term result because of the apparent involvement of the pulmonary vein from the right upper lobe. In the surviving patient, we shall perform pneumonectomy if his clinical condition worsens.

We describe two patients with congenital atresia of the pulmonary veins and confirm the value of isotope scans and pulmonary angiography in clarifying the diagnosis of this rare condition. The diagnosis should be considered in any child with recurrent unilateral pneumonia, especially if it is associated with haemoptysis and radiographic evidence of reduced lung volume on the affected side.

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Cross sectional echocardiographic identification of hypoplastic left heart syndrome and differentiation from other causes of right ventricular overload

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Abstract

To identify the echocardiographic features that can be used to distinguish between hypoplastic left heart syndrome and other causes of right ventricular overload in the sick neonate cross sectional echocardiographic studies of 10 neonates with hypoplastic left heart syndrome were analysed and compared with those in 15 neonates with other causes of right ventricular overload and 15 normal controls. Left ventricular and right ventricular cavity dimensions and the shape and size of the mitral valve annulus and aortic root were recorded and presented both as absolute values (mm) and corrected for body surface area (mm/m^2). Logistic regression was used to produce a classification rule to estimate the probability of a neonate having hypoplastic left heart syndrome. The diameter of the mitral valve annulus was the single most discriminative variable. There was, however, considerable overlap of all the calculated features between neonates with hypoplastic left heart syndrome and those with other causes of right ventricular overload.

The diagnosis of hypoplastic left heart syndrome should not be based on any one single echocardiographic feature but the general appearance of abnormal left heart valves, small cavity dimensions, and the size of the mitral valve annulus.

Cross sectional echocardiography has enhanced the diagnosis of congenital heart disease and in particular of cardiac abnormality in the newborn.[1] With conventional treatment, hypoplastic left heart syndrome is invariably fatal and must be distinguished early from potentially operable conditions which may have a similar clinical and echocardiographic presentation.

Previous reports identified the echocardiographic features of hypoplastic left heart syndrome: the main one is an abnormally small left ventricular cavity compared with the right ventricle.[2-7] Though some workers reported that associated cardiac abnormalities aided echocardiographic diagnosis,[5 8 9] the wide range of cardiac lesions in this syndrome[10] makes it difficult to distinguish between hypoplastic left heart syndrome and other causes of right ventricular dominance.

We sought to describe the range of cardiac abnormalities associated with hypoplastic left heart syndrome and to identify the echocardiographic variables that distinguish the sick neonate with hypoplastic left heart syndrome from infants with other causes of right ventricular overload.

Patients and methods

Hypoplastic left heart syndrome was diagnosed in 10 neonates referred to the cardiac ultrasound laboratory at the Hammersmith Hospital over a period of five years. In nine the diagnosis was confirmed at necropsy and in one patient at cardiac catheterisation and operation. This patient subsequently died and permission for a necropsy was refused (table 1).

We also studied 15 neonates with other causes of right ventricular overload (table 2) and 15 clinically normal neonates with similar age and body surface area (table 3).

METHODS

Complete echocardiographic studies were performed in all patients according to a well standardised protocol,[11] particular attention was given to imaging the right heart chambers from multiple views.[12] We used suprasternal and high parasternal views to image the aortic arch.[13] We used ATL Mark 100C ultrasound equipment with a 5 and a 7 MHz mechanical transducer or a Toshiba SSH 160A with a 3·75 MHz and a 5 MHz phased array transducer. In all neonates we used appropriate on-axis projections of right and left ventricles from parasternal long axis views to measure the maximum dimension of the left and right ventricular cavities and the thickness of the posterior left ventricular wall and interventricular septum. These measurements were taken at the level of the chordae tendineae (fig 1A). We used cross sectional short axis projections to measure the anteroposterior and lateral left ventricular diameters to assess possible geometric distortion of the left ventricle secondary to right ventricular overload (fig 1B). Aortic root dimensions were measured from the parasternal long axis projection, the maximum diameter being recorded at the sinus, sinotubular junction, and ascending aorta (fig 1C). The size of the mitral valve annulus was assessed from the apical four chamber projection (fig 1D).

All the chamber dimensions and mitral annulus diameter were measured at end diastole; the aortic root and ascending aorta were

Table 1 *Clinical and echocardiographic features of the 10 neonates with hypoplastic left heart syndrome*

Patient	Age at study (days)	Presenting symptom	Weight (kg)	BSA (m^2)	LV		SAX		RV		LVPW		IVS	
					(mm)	(mm/m^2)	(AP)(mm)	(LAT)(mm)	(mm)	(mm/m^2)	(mm)	(mm/m^2)	(mm)	(mm/m^2)
1	2	C, T, F	3·3	0·21	12	56·6	8	10	10	47·2	8	37·7	3	14·2
2	3	C, T, F	3·5	0·22	11	50·0	10	12	19	86·4	2	9·1	3	13·6
3	5	A, T, F	3·0	0·20	16	80·0	15	15	15	75·0	5	25·0	5	25·0
4	6	A, T, F	3·4	0·22	7	32·1	11	10	18	82·6	3	13·8	3	13·8
5	1	A, T, F	2·9	0·21	11	52·9	13	11	16	76·9	8	38·5	6	28·8
6	9	C, T, F	3·0	0·21	2	9·8	2	3	33	161·0	2	9·8	2	9·8
7	2	A, T	3·4	0·21	8	38·1	13	15	12	57·1	4	19·0	4	19·0
8	5	A, T, F	2·7	0·18	13	72·2	10	15	16	88·9	3	16·7	4	22·2
9	98	C, T	4·3	0·25	13	52·0	15	22	38	152·0	4	16·0	4	16·0
10	1	A, T, F	3·0	0·20	9	46·2	7	9	18	92·3	3	15·4	4	20·5
Mean	13		3·25	0·21	10·2	49·0			19·5	91·94	4·2	20·1	3·8	18·29
(1 SD)			0·45	0·02	3·9	19·8			8·95	36·9		10·49		5·89
Range														
Max	98		4·3	0·25	16	80·0			38	161·0	8	38·5	6	28·8
Min	1		2·7	0·18	2	9·8			10	47·2	2	9·1	2	9·8

A, acyanotic; Ao, aorta, Ao-S, aortic root at sinus level, Ao-ST, aortic root at sinotubular level, Ao-AA, ascending aorta, AP, anteroposterior; ASD, atrial septal defect. AV, aortic valve, BSA, body surface area, C, cyanosis; Coarctn, coarctation; CS, dilated coronary sinus; DA, ductus arteriosus, Desc, description; EFE, endocardial fibroelastosis, F, heart failure; IVS, interventricular septum; L, left, LAT, lateral, LV, left ventricle; LV contn, LV contraction, LVPW, posterior left ventricular wall, M0, imperforate; M1, minimal mobility; M2, mobile, Musc VSD, muscular ventricular septal defect, MV, mitral valve annulus; RV, right ventricle, RVH, right ventricular hypertrophy; SAX, short axis; SVC, superior vena cava; T, tachypnoea; TAPVD, total anomalous pulmonary venous drainage; Th, thickened.

Table 2 *Clinical and echocardiographic features of the 15 neonates with other causes of right ventricular overload*

Patient	Age at study (days)	Weight (kg)	BSA (m^2)	LV		SAX		RV		LVPW		IVS	
				(mm)	(mm/m^2)	(AP)(mm)	(LAT)(mm)	(mm)	(mm/m^2)	(mm)	(mm/m^2)	(mm)	(mm/m^2)
1	2	2·9	0·21	17	82·9	10	13	15	73·2	4	19·5	4	19·5
2	13	3·3	0·22	16	74·4	14	17	17	79·1	4	18·6	5	23·2
3	1	3·0	0·21	17	82·9	14	17	15	73·2	4	19·5	6	29·3
4	2	3·5	0·22	18	80·7	12	14	12	53·8	5	22·4	5	22·4
5	10	3·1	0·21	21	100·0	15	17	15	71·4	5	23·8	6	28·6
6	3	2·6	0·19	14	72·9	11	15	18	93·7	2	10·4	7	36·5
7	3	3·6	0·23	18	80·0	16	21	17	75·6	4	17·8	5	22·2
8	10	2·7	0·20	8	40·0	9	14	21	105·0	3	15·0	4	20·0
9	3	3·5	0·23	14	60·9	13	18	21	91·3	3	13·0	4	17·4
10	3	3·3	0·21	13	61·9	14	18	16	76·2	4	19·0	3	14·3
11	2	2·8	0·20	21	105·0	14	14	18	90·0	4	20·0	6	30·0
12	1	3·0	0·22	14	63·6	14	20	12	54·5	4	18·2	3	13·6
13	1	3·5	0·21	11	52·4	13	18	15	71·4	4	19·0	4	19·0
14	77	4·1	0·25	16	64·0	15	17	16	64·0	4	16·0	4	16·0
15	8	2·6	0·19	13	68·4	11	18	13	68·4	3	15·8	3	15·8
Mean	9	3·2	0·21	15·4	72·67			16·1	76·06	3·8	17·88	4·6	21·86
(1 SD)		0·43	0·02	3·5	16·97			2·7	14·16		3·42		6·63
Range													
Max	77	4·1	0·25	21	105·0			21	105·0	5	23·8	7	36·5
Min	1	2·6	0·19	8	40·0			12	53·8	2	10·4	3	13·6

dTGA, transposition of the great arteries; N, normal. Other abbreviations as in table 1

Table 3 *Echocardiographic features of the 15 control neonates*

Patient	Age at study (days)	Weight (kg)	BSA (m^2)	LV		SAX		RV		LVPW		IVS	
				(mm)	(mm/m^2)	(AP)(mm)	(LAT)(mm)	(mm)	(mm/m^2)	(mm)	(mm/m^2)	(mm)	(mm/m^2)
1	14	4·1	0·24	17	72·3	17	17	8	34·0	4	17·0	4	17·0
2	10	3·8	0·23	15	65·8	17	16	8	35·1	4	17·5	4	17·5
3	11	1·8	0·17	17	101·2	17	17	7	41·7	4	23·8	5	29·8
4	14	3·9	0·23	17	73·3	18	17	11	47·4	4	17·2	5	21·6
5	5	3·3	0·22	15	69·8	15	15	10	46·5	3	14·0	4	18·6
6	10	3·0	0·21	16	76·6	15	16	7	33·5	4	19·1	4	19·1
7	60	3·7	0·23	14	60·9	16	18	8	34·8	3	13·0	3	13·0
8	1	2·0	0·14	12	88·9	8	9	7	51·9	4	29·6	4	29·6
9	7	3·1	0·20	18	92·3	13	18	12	61·5	3	15·4	3	15·4
10	12	3·1	0·20	15	76·9	14	19	12	61·5	4	20·5	3	15·4
11	2	2·7	0·20	13	65·0	14	15	8	40·0	4	20·0	4	20·0
12	9	3·4	0·22	15	68·2	14	14	14	63·6	5	22·7	5	22·7
13	15	3·4	0·22	19	86·4	15	15	11	50·0	3	13·6	3	13·6
14	72	3·3	0·25	12	48·0	18	13	15	60·0	4	16·0	3	12·0
15	38	2·0	0·14	13	96·3	12	12	7	51·9	3	22·2	3	22·2
Mean	19	3·1	0·20	15·2	76·12			9·7	47·56	3·7	18·79	3·8	19·18
(1 SD)		0·7	0·04	2·1	14·51			2·7	10·82		4·50		5·38
Range													
Max	72	4·1	0·25	19	101·2			15	63·6	5	29·6	5	29·8
Min	1	1·8	0·14	12	48·0			7	33·5	3	13·0	3	12·0

MV		*MV desc*	*Ao-S*		*Ao-ST*		*Ao-AA*		*AV desc*	*LV contn (1–3)*	*Other features*
(mm)	*(mm/m²)*		*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*			
4	18·9	Th, M1	3	14·2	3	14·2	3	14·2	Th, M1	1	Th posterior wall, musc VSD, RVH, DA
5	22·7	M1	3	13·6	3	13·6	3	13·6	M2	1	RVH
8	40·0	M2	5	25·0	6	30·0	9	45·0	M2	2	Musc VSD, RVH
4	18·3	M1	3	13·8	3	13·8	5	22·9	Th, M1	1	RVH
0	0	M0	5	24·0	5	24·0	5	24·0	M2	1	Th posterior wall, bicuspid AV, RVH
0	0	M0	4	19·5	4	19·5	5	24·4	M0	1	LV slit like cavity, RVH, ASD, DA
4	19·0	Th, M1	2	9·5	2	9·5	3	14·3	M0	1	RVH, DA
6	33·3	M2	6	33·3	4	22·2	5	27·8	M2	2	DA, ASD, RVH, very dilated main PA, L SVC to CS
10	40·0	M2	8	32·0	7	28·0	8	32·0	M2	3	TAPVD, RV:EFE
5	25·6	M2	3	15·4	8	41·0	8	41·0	Th, M1	2	Ao coarctn + DA repaired
5·8	27·3		4·2	20·03	4·5	21·58	5·4	25·92			
2·2	9·3		1·8	8·21	1·96	9·57	2·22	10·91			
10	40·0		8	33·3	8	41·0	9	45·0			
0	18·3		2	9·5	2	9·5	3	13·6			

MV		*MV desc*	*Ao-S*		*Ao-ST*		*Ao-AA*		*AV desc*	*LV contn (1–3)*	*Diagnosis*
(mm)	*(mm/m²)*		*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*			
9	43·9	N	7	34·1	7	34·1	7	34·1	N	3	TAPVD, CS
10	46·5	N	6	27·9	6	27·9	6	27·9	N	3	VSD (subarterial), subaortic stenosis, Ao coarctn, CS
10	48·8	N	10	48·8	11	53·7	11	53·7	N	3	dTGA, RVH, CS
10	44·8	N	10	44·8	10	44·8	10	44·8	N	3	Ebstein, musc VSD
12	57·1	N	8	38·1	9	42·9	11	52·4	N	3	Ao coarctn, musc VSD
10	52·1	N	8	41·7	7	36·5	8	41·7	N	3	Persistent fetal circulation
12	53·3	N	9	40·0	9	40·0	11	48·9	N	3	TAPVD
8	40·0	N	7	35·0	6	30·0	7	35·0	N	3	TAPVD, impaired RV function
9	39·1	N	6	26·1	6	26·1	7	30·4	N	3	ASD
11	52·4	N	7	33·3	6	28·6	6	28·6	N	3	Ao coarctn
9	45·0	N	10	50·0	10	50·0	10	50·0	N	3	dTGA
9	40·9	N	8	36·4	7	31·8	8	36·4	N	3	TAPVD
11	52·4	N	9	42·9	8	38·1	10	47·6	N	3	VSD, ASD
13	52·0	N	11	44·0	10	40·0	11	44·0	N	3	dTGA (VSD + ASD)
8	42·1	N	9	47·4	9	47·4	8	42·1	N	3	ASD
10·1	47·37		8·3	39·36	8·1	38·12	8·7	41·17			
1·5	5·63		1·5	7·25	1·8	8·48	1·9	8·63			
13	57·1		11	50·0	11	53·7	11	53·7			
8	39·1		6	26·1	6	26·1	6	27·9			

MV		*Ao-S*		*Ao-ST*		*Ao-AA*	
(mm)	*(mm/m²)*	*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*	*(mm)*	*(mm/m²)*
10	42·6	9	38·3	7	29·8	9	38·3
8	35·1	7	30·7	8	35·1	8	35·1
11	65·5	8	47·6	7	41·7	7	41·7
12	51·7	9	38·8	8	34·5	10	43·1
9	41·9	9	41·9	8	37·2	10	46·5
11	52·6	8	38·3	8	38·3	9	43·1
10	43·5	8	34·8	8	34·8	8	34·8
12	88·9	6	44·4	7	51·9	8	59·3
12	61·5	6	30·8	5	25·6	7	35·9
11	56·4	7	35·9	6	30·8	6	30·8
8	40·0	6	30·0	8	40·0	7	35·0
10	45·5	9	40·9	9	40·9	10	45·5
10	45·5	9	40·9	9	40·9	10	45·5
10	40·0	8	32·0	7	28·0	9	36·0
7	51·9	7	51·9	7	51·9	8	59·3
10·1	50·83	7·7	38·47	7·5	37·42	8·3	41·97
1·5	13·51	1·16	6·41	1·1	7·64	1·3	8·43
12	88·9	9	51·9	9	51·9	10	59·3
7	35·1	6	30·0	5	25·6	6	30·8

measured at end systole. For each, three measurements were taken from three successive cardiac cycles. The mean value was expressed as an absolute value (mm) and corrected for body surface area (mm/m²).

To assess the degree of geometric distortion of the ventricular cavity, we measured the percentage difference between the anteroposterior and lateral dimensions of each left ventricular cavity in the short axis projection. These percentages were used an an index of distortion; the value for a perfect circle is 0%.

Left ventricular systolic function was assessed from the real time image by two observers experienced in neonatal studies. Each blindly reviewed all the studies from the three groups. Systolic contraction, evaluated from the serial short axis left ventricular

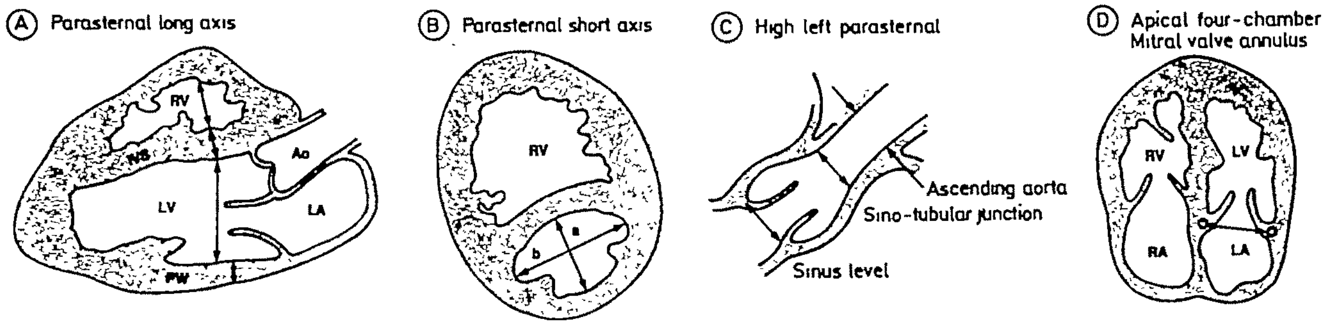

Figure 1 Diagrammatic representation of the measurements made. (A) Parasternal long axis projection at end diastole. (B) Cross sectional short axis projection at end diastole. (C) Parasternal long axis projection of the aortic root at end systole. (D) Apical four chamber projection.

projections, was graded from 1 to 3 (1 = negligible contractile function; 2 = reduced but fair systolic contractile motion; and 3 = normal contractile function). Disagreement between observers was settled reaching a consensus after a joint review of the study in question.

Tables 1 and 2 show the associated congenial heart defects.

STATISTICAL ANALYSIS

All results are corrected for body surface area, and dimensions are quoted as mean (1 SD). We compared the samples using Student's *t* distribution. A probability value of $<0{\cdot}05$ was regarded as significant.

We used logistic regression to produce a classification rule based on the dimension of the left ventricular cavity, mitral valve annulus, and aortic root to estimate the probability of a neonate having hypoplastic left heart syndrome. Such a rule can be formed from any set of the measurements taken and the more informative a set of measurements is the better will be the classification rule obtained from it.

To assess the performance of a classification rule one could simply count the number of neonates correctly classified, but this does not measure the uncertainty with which each individual has been classified. Such information is provided by a statistic known as the deviance.[14] When a number of measurements are added to the rule, the greater the decrease in the deviance, the greater the improvement in the rule. Significance was assessed by referring the decrease in deviance to the χ^2 distribution with degrees of freedom equal to the number of measurements added. The analysis was carried out using the statistical package *Generalised Linear Interactive Modelling*.[15]

Results

In all individuals (patients and controls) echocardiograms were good enough to show the complete intracardiac anatomy. Tables 1 and 2 summarise the clinical features of the 10 neonates with hypoplastic left heart syndrome and the 15 neonates with other causes of right ventricular overload. Cardiac failure was the major presenting symptom in both groups; six (60%) of the neonates with hypoplastic left heart syndrome were acyanotic.

CROSS SECTIONAL ECHOCARDIOGRAPHIC FEATURES

Left ventricular cavity (fig 2)

Although patients with hypoplastic left heart syndrome had smaller left ventricular cavities than patients with other causes of right ventricular overload ($p < 0{\cdot}005$) and the normal individuals ($p < 0{\cdot}001$) as a whole, there was a considerable overlap of individual values among the three groups.

There was no significant difference in the degree of distortion between the patients with hypoplastic left heart syndrome and those with other causes of right ventricular overload (25·4%, 95% confidence interval 12·1 to 38·7) compared with 29·9% (20·6 to 39·2). The normal controls showed much less distortion (10·9%, 2 9–18·9).

In all but one neonate with hypoplastic left heart syndrome left ventricular contractile function was poorer than in the subjects with right ventricular overload, all of whom had normal function (tables 1 and 2).

Right ventricular cavity size (fig 2)

In patients with hypoplastic left heart syndrome the size of the right ventricular cavity was similar to that in patients with other causes of right ventricular overload. In both groups, however, the diameter was greater than that in the controls ($p < 0{\cdot}001$).

Mitral valve annulus (fig 2)

The mitral valve annulus was smaller in patients with hypoplastic left heart syndrome than in patients with other causes of right ventricular overload ($p < 0{\cdot}001$) and in the controls ($p < 0{\cdot}001$). Only two neonates with hypoplastic left heart syndrome had a mitral valve annulus within the range of values for the group with right ventricular overload and controls, while in two other patients with hypoplastic left heart syndrome the mitral valve was clearly imperforate.

Aorta (fig 3)

The dimensions of the aortic root and ascending aorta were smaller in patients with hypoplastic left heart syndrome than in those with right ventricular overload ($p < 0{\cdot}001$), though there was a considerable spread of values. This spread was also seen in the control group.

Appearance of the aortic and mitral valves

Seven (70%) of the neonates with hypoplastic left heart syndrome had abnormalities of the aortic and mitral valves ranging from imperforate valves (two of 10) to thickened valves with reduced mobility (four of 10); in three patients both the left heart valves were of normal appearance. One of these three had coexistent supracardiac total anomalous pulmonary venous drainage with obstruction (patient 9). These findings were confirmed at necropsy.

No patient with a right ventricular loading condition had a morphologically abnormal mitral or aortic valve.

Wall thickness (tables 1–3)

Left ventricular wall thickness was generally similar in the three groups of patients. Two patients (1 and 5) with hypoplastic left heart syndrome showed considerable thickening of the posterior wall (fig 4). This feature was noted at necropsy and described as fibroelastic thickening.

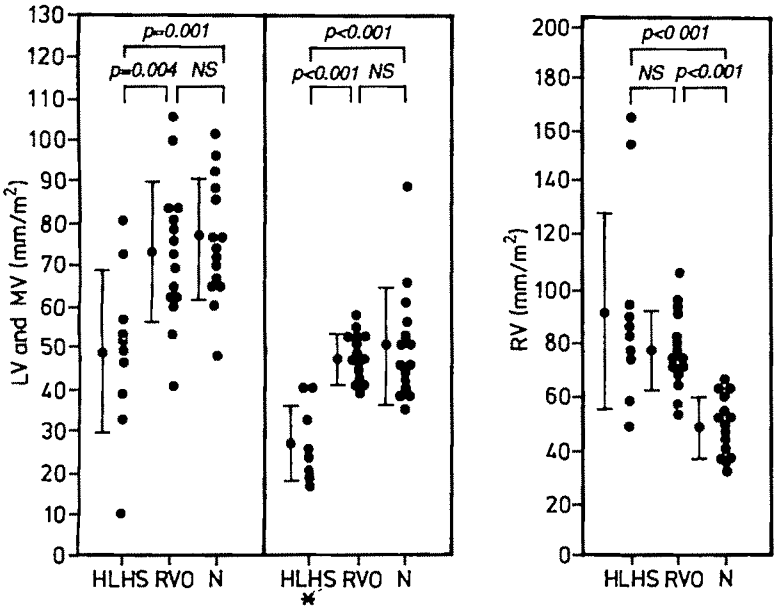

*Figure 2 Comparative values and mean (1 SD) for the neonates with hypoplastic left heart syndrome (HLHS), right ventricular overload (RVO), and normal neonates (N) at left ventricular (LV), mitral annulus (MV), and right ventricular (RV) levels. *Two HLHS patients had imperforate mitral valves.*

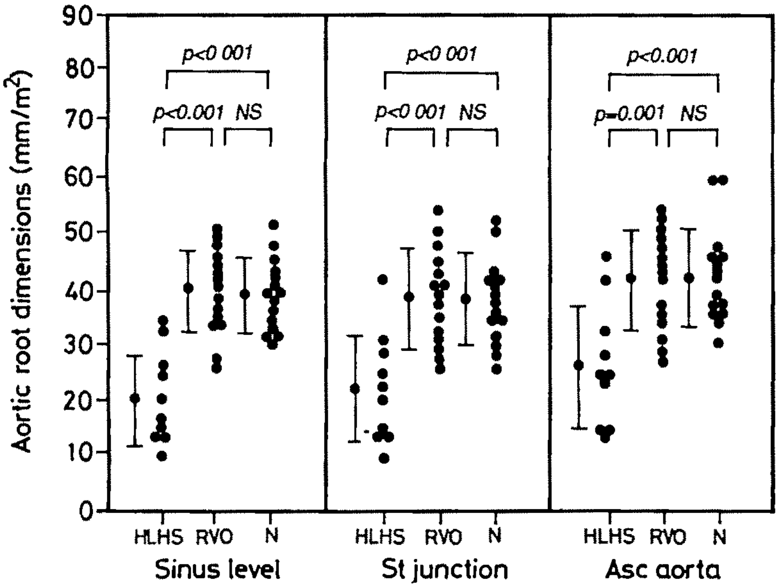

Figure 3 Comparative values and means (1 SD) for aortic root dimensions at the sinus level, the sinotubular junction (St), and in the ascending aorta (Asc aorta).

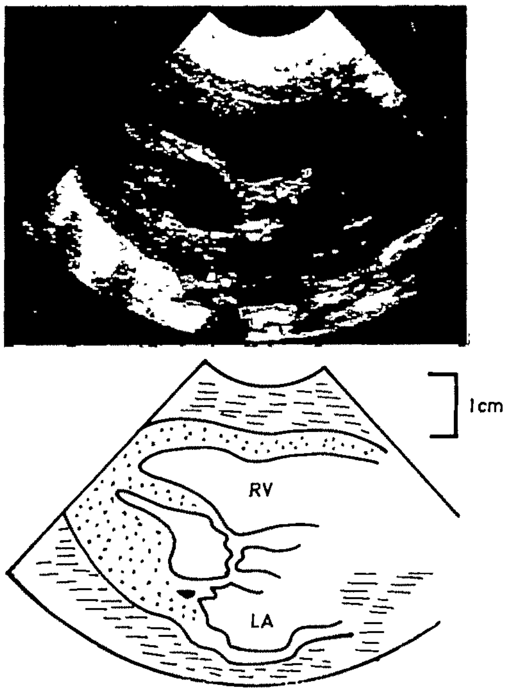

Figure 4 Parasternal long axis view in patient 5 with hypoplastic left heart syndrome showing the thickened appearance of the posterior wall.

Associated lesions (table 1)

In four of the patients with hypoplastic left heart syndrome there were additional malformations that could have produced right ventricular loading. Patient 9 had total anomalous pulmonary venous drainage with obstruction, two others (patients 6 and 8) had secundum atrial septal defects, and one (patient 10) had an aortic coarctation.

Statistical analysis

Logistic regression showed that the diameter of the mitral valve annulus was the single best measurement for distinguishing patients with hypoplastic left heart syndrome from either healthy controls or those with other causes of right ventricular overload. It correctly identified 37 of the 40 neonates (fig 5). The diameter of the aortic root at sinus level was the only other single measurement that correctly classified as many as this, but the deviance was greater (15 79 compared with 12·33), indicating a less good fit to the data—as was evident from the histogram of estimated probabilities (fig 5).

Of all the rules that used two measurements, none misclassified less than three individuals, although the rule using mitral valve annulus, aortic root measurement at the sino-tubular junction, and the dimension of the ascending aorta misclassified only one. However, the decrease in deviance from the model using only mitral valve annulus diameter was 5·15%, which when referred to a χ^2 distribution with 2 degrees of freedom is not significant at the 5% level. This indicates that such an improvement in the classification rule could well have arisen by chance. No rule classified all 40 neonates correctly.

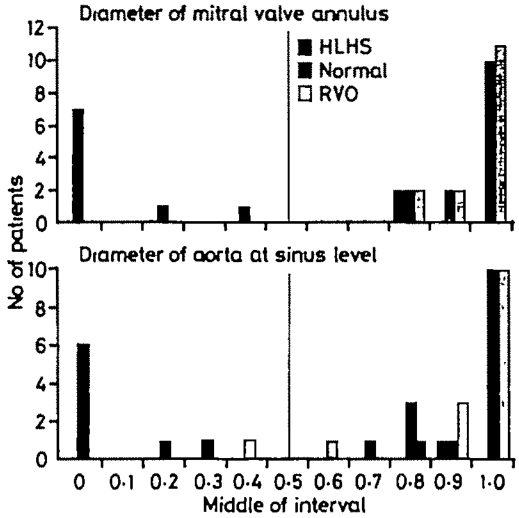

Figure 5 Histograms of estimated probabilities when the diameter of the mitral annulus (top) and the diameter of the aortic root (bottom) were used as discriminants. Patients lying between probability intervals 0 and 0 5 are classified as having hypoplastic left heart syndrome (HLHS). Patients lying between 0·5 and 1 0 are classified as normal or as having another cause for right ventricular overload (RVO).

The fewer the number of measurements used, the less likely it is that the rule is reflecting "artefacts" in the particular dataset from which it is constructed—that is the more applicable it is likely to be to other situations. Because the correct classification rate was based on the same data as we used to derive the classification rule, this will tend to overestimate the accuracy of the approach. One way of reducing this effect is the "jack-knife" or "leaving-one-out" technique.[16 17] Each neonate in turn was left out of the dataset and it was classified according to the rule based on the remaining 39. When we used this technique with the rule that used the dimension of the mitral valve annulus, the same three neonates as before were misclassified, and no others. This is an indication that the other 37 neonates were classified correctly with a high degree of confidence.

We concluded that using mitral valve annulus dimension alone gives the best classification rule. When we used this rule, the estimated probability of a neonate having hypoplastic left heart syndrome was:

$$\frac{1}{1 \times e^{[-15\cdot5 + \{0\cdot428 \times MV\}]}}$$

where MV is the mitral valve annulus size in mm/m^2. According to this rule, a neonate will be deemed to have hypoplastic left heart syndrome if the estimated probability is greater than 0·5. This corresponds to the dimension of a mitral valve annulus being $<36\cdot3$ mm/m^2. If, for example, the mitral valve annulus was 30 mm/m^2 then the estimated probability of a neonate having hypoplastic left heart syndrome was 0 93.

Discussion

Though hypoplastic left heart syndrome accounts for between 1·5% and 9% of congenital heart defects, it is responsible for up to 22% of deaths in the first month of life.[1]

The echocardiographic recognition of hypoplastic left heart syndrome is primarily based on the detection of small left heart structures. Often, however, it is unclear whether the left ventricle is "small", or merely appears so because it is compressed and displaced by a dilated right ventricular cavity (fig 6).

At present there are no echocardiographically measured standard dimensions below which a left ventricle is classified as "hypoplastic" and no systematic comparison has been made between the cross sectional echocardiographic features of hypoplastic left heart syndrome and other causes of right ventricular overload—most studies made comparisons with a healthy population.[3 5]

Farooki *et al* described the echocardiographic features of hypoplastic left heart syndrome based on M mode echocardiography alone and, comparing these measurements with those from a normal population, derived the following distinguishing criteria: left ventricular dimension <9 mm, aortic root diameter <6 mm, ratio of left ventricular to right ventricular dimension of <0·6, and, finally, an absent or greatly distorted mitral valve echogram.[3] When these criteria were applied to our data they were shown to be insensitive, particularly the left ventricular dimensions and the left ventricular to right ventricular ratio. These measurements identified four of 10 and five of 10 of the patients with hypoplastic left heart syndrome respectively.

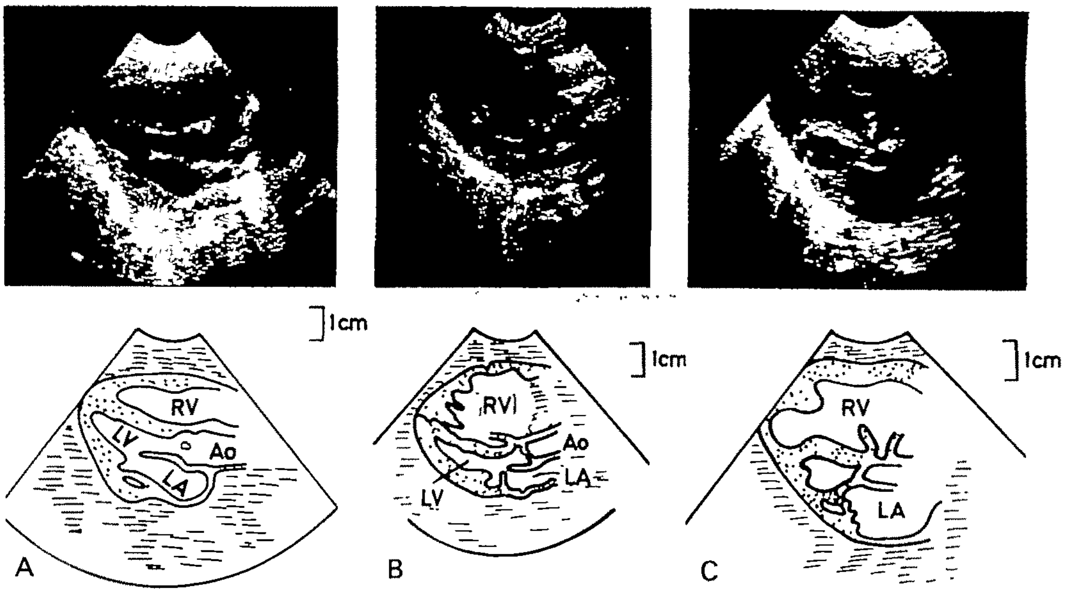

Figure 6 Parasternal long axis views comparing a normal neonate (A) with a neonate with right ventricular overload (B) and a neonate with hypoplastic left heart syndrome (C).

The limitations of M mode echocardiographic measurements in the diagnosis of hypoplastic left heart syndrome have also been highlighted by Lange *et al* who assessed M mode echocardiographic, cross sectional echocardiographic, and necropsy correlations.[18] They found that the range of hypoplastic left heart syndrome was too great to be resolved by M mode echocardiographic measurements alone, but the correlation between cross sectional echocardiography and postmortem findings was close.

In our study the variability in left ventricular cavity dimension in hypoplastic left heart syndrome measured from cross sectional studies was too great to distinguish between this condition and other causes of right ventricular overload or between the normal controls. Only three of the 10 neonates with hypoplastic left heart had left ventricular cavity sizes outside the range of the group with right ventricular loading.

The dimension of the aortic root at sinus level was a more discriminative variable; however, coexistent aortic coarctation or an interrupted aortic arch will cause diagnostic confusion as reported by Lange *et al.*[18] This condition did not occur in our population. The diameter of the mitral valve annulus was the most discriminative single variable and correctly classified all but three of the 40 neonates.

In our series, the three patients with morphologically normal left heart valves posed the most difficult diagnostic challenge. In one of these (patient 8), cross sectional echocardiographic findings were suggestive of total anomalous pulmonary venous drainage; only at operation was hypoplastic left heart syndrome diagnosed, the pulmonary veins draining normally. In another (neonate 3), despite a hypoplastic aortic root, all other chamber dimensions fell in the range of values found in patients with right ventricular overload. A comparison of the anteroposterior and lateral left ventricular cavity dimensions in the short axis projection did not show any difference in the amount of geometric distortion between patients with hypoplastic left heart syndrome and those with other causes of right ventricular overload.

We conclude that no single echocardiographic feature was diagnostic of hypoplastic left heart syndrome. Furthermore, the presence of associated lesions that tend to cause right ventricular overload in their own right may add to the diagnostic difficulty.

A positive diagnosis of hypoplastic left heart syndrome can be made with a high degree of accuracy if it is based on a constellation of echocardiographic features which include (*a*) the size of the mitral valve annulus and mitral valve mobility, (*b*) the size of the aortic root and aortic valve mobility, and (*c*) the size and function of the left ventricle.

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Balloon dilatation of critical stenosis of the pulmonary valve in neonates

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Abstract
Percutaneous balloon dilatation was attempted in 15 consecutive neonates (mean age 7·3 (range 1–27) days and weight 3·2 (range 2·5–4·1) kg) with critical stenosis of the pulmonary valve. Dilatation was successful in 11 (73%) patients. The mean balloon to annulus ratio was 1·1 (range 0·6–1·77). The ratio of right ventricle to femoral artery systolic pressure decreased from a mean (1 SD) of 1·4 (0·32) before to 0·8 (0·24) after dilatation and the transvalvar gradient decreased from 81 (29·7) mm Hg before to 33 (27·7) mm Hg after dilatation. All four (27%) patients in whom dilatation was unsuccessful underwent surgical valvotomy. Complications of balloon dilatation occurred in three (20%) patients; these included retroperitoneal haematoma (one) and iliofemoral venous occlusion (two). In one (7%) patient severe hypoxia and hypotension developed when the valve was crossed with a guide wire and balloon catheter. Despite successful dilatation he died 7 days after the procedure. During a mean (1 SD) follow up of 2 (1·7) years, seven (64%) of the 11 patients remained free of important restenosis. One patient required repeat dilatation three weeks after the initial procedure. In three (27%) patients restenosis developed 4–9 months after dilatation and all three had surgical valvotomy. Of the four patients initially referred for surgery three required a second operation and one required balloon dilatation.

Percutaneous balloon dilatation gave effective relief of critical pulmonary stenosis in most neonates but complications and restenosis requiring surgery were common.

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Since successful balloon dilatation of the stenotic pulmonary valve was first described,[1] several studies have shown its safety and efficacy in infants and children.[2-4] When large enough balloons were used for dilatation, acceptable reductions in transvalvar gradients were obtained. The results compared favourably with those of valvotomy.[5 6] In these age groups most centres prefer balloon dilatation for the treatment of valvar pulmonary stenosis.

Balloon dilatation is also possible in neonates with critical stenosis of the pulmonary valve,[2] but may be associated with more haemodynamic disturbances and may be less well tolerated, especially if the ductus arteriosus has closed. So far only short term results have been reported in small numbers of patients.[7 8] We report our experience with 15 consecutive neonates with critical stenosis of the pulmonary valve in whom this treatment was attempted.

Patients and methods

PATIENTS

Since November 1983 we have attempted percutaneous balloon dilatation of the pulmonary valve in 15 consecutive neonates with critical stenosis of the pulmonary valve. The average age at cardiac catheterisation was 7·3 days (median age 4 days, range 1–27) and mean weight 3·2 (range 2·5–4·1) kg. The diagnosis was established antenatally by cross sectional echocardiography in five (33%) patients. In all the clinical diagnosis was confirmed by postnatal cross sectional and Doppler echocardiography. All patients were cyanosed and 13 were treated with prostaglandin E_2 infusion before catheterisation.

TECHNIQUE OF CARDIAC CATHETERISATION AND BALLOON DILATATION

Cardiac catheterisation and balloon dilatation were performed under general anaesthesia in eight patients and under local anaesthesia with intravenous ketamine in the remainder. A full preliminary diagnostic catheterisation was performed via a percutaneous femoral vein puncture. Arterial pressure was monitored continuously by either femoral, umbilical, radial, or brachial arterial lines. A right ventricular angiogram was performed and recorded in the anteroposterior or the left lateral projections or both. The diameter of the pulmonary valve annulus was then measured from the lateral cineangiogram at the level of the attachment of the valve leaflets. We corrected this measurement for the magnification of the angiogram by reference to the external diameter of the angiography catheter. Then we selected a balloon catheter that was appropriate for the corrected annulus size. During the initial period of the study we used balloons with a diameter equal to or somewhat larger than the annulus. Subsequently we used balloons 20%–40% bigger than the annulus. The ductus arteriosus was open in 13 patients, though it was only small in five of them.

The pulmonary valve was crossed by standard 0·020 inch (two patients) or 0·018 inch (four patients) guide wires (William Cook Europe) and 4 or 5 French multipurpose end hole catheters. In the latter half of the study period when it was not possible to cross the valve with the standard guide wires we used a "super floppy" or "steerable" exchange guide wire (Schneider Shiley UK, 0·018–0·020 inch diameter) in five patients before abandoning the attempt. Once the end hole catheter was across the valve we used it to pass an exchange wire of a diameter appropriate for the balloon catheter. In seven patients the guide wire was positioned in the peripheral left pulmonary artery, in one patient in the right pulmonary artery, and in three through the ductus arteriosus. In one patient a guide wire (standard 0·018 inch wire) could not be passed to a stable position. In three patients with angiographically dysplastic valves the pulmonary valve was not crossed (in two with standard guide wires and in one patient with additional Ebstein's anomaly a "steerable" wire was used).

When the guide wire was in a satisfactory position the end hole catheter and venous sheath were removed and the balloon dilatation catheter was passed over the wire (Schneider Shiley UK, Mansfield Scientific, and Meadox Surgimed USA). We used still frames from the angiograms as a guide to placing the balloon catheter with its mid-point across the valve. The balloon was then inflated with dilute contrast medium until the constriction caused by the stenosed pulmonary valve disappeared. The inflation-deflation cycle lasted 15–20 s. After balloon dilatation the balloon catheter was exchanged for a Goodale-Lubin catheter to measure the transvalve withdrawal gradient and right ventricular pressure. Repeat angiography was not routinely performed. The mean length of the procedure was 2·4 (range 1·1–3·9) hours. The mean duration of *x* ray screening was 34·8 minutes (range 10–57 minutes). In patients in whom dilatation was successful, the mean (1 SD) annulus diameter was 7·4 (1·6) mm. The diameter of the balloons used ranged from 3 to 10 mm. The maximum balloon to annulus ratios ranged from 0·63 to 1·77 (mean 1·1 (0·28)).

BALLOON DILATATION IN STEPS

Only one balloon was used in seven patients. In the last four patients, because it was impossible to pass a 5 French catheter through the valve without causing hypotension and hypoxia, preliminary dilatation was performed with 3–5 mm low profile coronary angioplasty balloon catheters on 3 7–4·3 French shafts to reduce haemodynamic disturbance and ease the subsequent passage of the larger balloon catheters (fig 1A, B, and C). The details of this technique have been reported elsewhere in a different group of patients.[9] In those undergoing dilatation in steps two balloons were used in one patient, three balloons in two, and four balloons in one patient. The final balloon diameters used ranged from 9 to 10 mm and the balloon to annulus ratios achieved ranged from 1·0 to 1·77.

STATISTICAL ANALYSIS

Data are presented as mean values (1 SD). Differences between variables before and after balloon dilatation were assessed by Student's *t* test for paired data.

Results

BALLOON DILATATION

The pulmonary valve was successfully dilated in 11 patients. In three patients with dysplastic valves, one of whom also had Ebstein's anomaly, the valve could not be crossed. Though the valve was crossed in another patient, the guide wire could not be passed to a stable position in either the left or right pulmonary arteries and thus the valve could not be dilated. All four of these patients had surgical valvotomy.

HAEMODYNAMIC RESULTS

The table summarises the haemodynamic changes. There was a significant decrease in right ventricular pressure, in the right ventricular to systemic pressure ratio, and in the transvalvar systolic gradients after balloon dilatation.

COMPLICATIONS

One patient (7%) died 7 days after balloon dilatation. There were no late deaths. This patient, aged 3 days, had severe pulmonary stenosis and duct-dependent pulmonary circulation. When the pulmonary valve was crossed with the guide wire and catheter and the catheter was placed in the descending aorta through the arterial duct severe hypotension and hypoxia developed which required removal of the catheter, cardiopulmonary resuscitation, and inotropes. Successful dilatation was subsequently performed with a low profile 5 mm balloon, but when we attempted to pass a larger balloon the iliac vein was dissected causing a large retroperitoneal haematoma. Though initially the patient was haemodynamically stable after the dilatation, with a Doppler estimated residual pulmonary gradient <16 mm Hg, epileptic seizures developed and ultrasound examination showed multiple intracerebral haemorrhages. He became neurologically unresponsive and died 7 days after balloon dilatation.

Minor immediate complications included transient bradycardia and hypotension on balloon inflation in all the patients. After successful dilatation of the pulmonary valve in one patient it proved difficult to withdraw the balloon catheter from the groin. On removal of the catheter a ring of vascular tissue was found wrapped around the mid-portion of the balloon. Contrast injection into the femoral vein showed a patent but irregular lumen with no extravasation of contrast material. The leg showed considerable venous congestion immediately after the procedure which resolved completely over 48 hours.

The long flexible tip of a "super-floppy" results show that balloon dilatation is an effective form of emergency treatment.

Balloon dilatation in neonates is often a technically difficult procedure but is associated with fewer risks than surgical operation. Several modifications in the technique are needed to reduce the occurrence of complications. Before balloon dilatation, prostaglandin E_2 infusion is maintained and the patient is stabilised haemodynamically (if necessary inotropes are also used). Goodale-Lubin and other end hole 4 or 5 French catheters are used to attempt to cross the pulmonary valve. This is often the most difficult part of the procedure. We now routinely attempt to cross the valve with "super-floppy" or "steerable" guide wires of 0·014, 0·018, or 0·020 inch diameter (Schneider-Shiley). These reduce the risk of infundibular trauma and can reduce the time needed to cross the valve. Since "steerable" guide wires became available we have failed to cross the valve in only one of the last nine patients. This patient had additional Ebstein's anomaly. Occasionally it is difficult to position the guide wire in either of the branch pulmonary arteries. Then the wire is passed through the ductus arteriosus and positioned in the descending aorta. The use of the ductus arteriosus may compromise pulmonary blood flow and result in haemodynamic deterioration; therefore speedy initial dilatation is essential. If the 5 French end hole catheter cannot be passed easily across the valve, then a coronary angioplasty balloon catheter of 3–3·5 mm diameter and 3·7 French shaft is used for the initial dilatation. This is followed by stepwise dilatation with larger balloon catheters to achieve the required balloon size.[9]

After dilatation the patient is weaned from the ventilator and prostaglandin E_2 while the arterial oxygen saturation is monitored. When desaturation persists and the right ventricular cavity is small prostaglandin E_2 infusion is continued for several days. Occasionally we have also used epoprostenol infusion to reduce the pulmonary vascular resistance. None of our patients required a systemic-to-pulmonary artery shunt.

In previous studies a dysplastic valve was regarded as a contraindication to balloon dilatation.[2 13 18] Most stenotic pulmonary valves in the neonate, however, seem dysplastic on echocardiography and angiography. They range from thin mobile leaflets with "pure" commissural fusion to valves with mixed dysplasia and commissural fusion and to the severely dysplastic valve with thickened valve leaflets attached to a hypoplastic "ring" showing little expansion in systole.[19] It is the degree of commissural fusion that probably determines the response to balloon dilatation, because disruption of commissural fusion by the balloon is thought to be the mechanism of relief of the obstruction.[20] One study has suggested that the degree of commissural fusion can be assessed from echocardiographic and angiographic appearances.[21] In neonates with critical stenosis of the pulmonary valve we do not believe that this can be determined with confidence. In this situation, where any reduction in pulmonary valve gradient and improvement of pulmonary flow is valuable, we have performed balloon dilatation irrespective of the angiographic appearances, recognising that surgery may eventually be necessary.

Complications such as iliofemoral venous occlusion may prevent repeat balloon dilatation. We now routinely give heparin (50 U/kg) to patients before balloon dilatation. This and the use of balloons on smaller French size shafts may reduce venous occlusion.

All the procedures lasted 2–4 hours and the fluoroscopy time ranged from 25 to 57 minutes. A similar period of fluoroscopy (30–68 minutes) was reported by Zeevi *et al.*[8] The duration of fluoroscopy is a potential risk to these babies because the dose of radiation received during the long screening times required for successful dilatation is not known. Fletcher *et al* calculated the radiation doses received by neonates during routine radiography and estimated the risks of malignant disease from fluoroscopy in different situations.[22] The risk of malignant disease was thought to be as high as 1 in 150 for some routine catheterisations compared with 1 in 280 000 for a single chest or abdominal radiograph. This is an overestimate of the risks of catheterisation because it was assumed that the risks for limited body exposures were the same as for whole body exposures. Nevertheless, the actual dose received by the neonates should be measured by skin dose meters. This may be an important factor to consider in the risk-benefit equation when balloon dilatation is compared with surgical valvotomy.

Although good initial results in infants can be obtained with balloons that are undersized in relation to the pulmonary annulus, the incidence of restenosis is high.[23] Our series confirms this in the neonate also. Restenosis requiring further treatment developed in 60% of the patients with balloon/annulus ratios $< 1\cdot0$ and in 14% in whom the balloon/annulus ratio was $> 1\cdot0$. As in older children balloon/annulus ratios of $> 1\cdot2$ give more satisfactory results.[5 23] To achieve such ratios safely, we recommend progressive balloon dilatation to reduce the incidence of haemodynamic complications.[9]

While large balloon/annulus ratios are aimed for, too large a balloon/annulus ratio may be associated with complications. Ring *et al* showed that when balloons $> 150\%$ of the annulus size were used in newborn lambs there was an increased incidence of subendocardial haemorrhage affecting the right ventricular free wall and outflow tract caused by trauma from the proximal end of the balloon straightening against the curvature of the outflow tract.[24] In clinical studies of older children Radtke *et al* showed that balloons 30%–60% bigger than the annulus size could be used safely to produce greater reductions in gradient than those associated with smaller balloons.[5] Furthermore, the frequency of recurrence of pulmonary valve stenosis requiring further treatment was higher for balloon/annulus ratios $< 1\cdot2$ than for ratios $> 1\cdot2$.[23] No benefit in terms of an immediate reduction in gradient or frequency of recurrence of stenosis was shown for ratios > 1·5.

We believe that balloon dilatation, rather than valvotomy, is the best treatment for neonatal critical pulmonary stenosis. It may be associated with a lower morbidity and mortality than surgical treatment. Restenosis may occur and is related to the use of undersized balloons. Other risks—for example the radiation dose of fluoroscopy—and the long term results when large balloon/annulus ratios are used, need further evaluation.

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Br Heart J 1990;63:368–9

CASE REPORTS

Right sided endocarditis after balloon dilatation of the pulmonary valve

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Abstract

A patient in whom infective endocarditis affecting the pulmonary and tricuspid valves developed after percutaneous balloon dilatation of the pulmonary valve is reported.

Percutaneous balloon dilatation is an effective and safe treatment for pulmonary valve stenosis.[1] We report a case of infective endocarditis of the pulmonary and tricuspid valves after balloon dilatation of a stenosed pulmonary valve.

Case report

A 38 year old woman presented in exertional dyspnoea (New York Heart Association class III). She was found to have severe stenosis of the pulmonary valve. Echocardiography showed a thickened and doming pulmonary valve. She underwent balloon dilatation. Four inflations were performed with a Mansfield, 9 French, 25 mm diameter, 3 cm long balloon catheter. The systolic pulmonary gradient fell from 194 to 63 mm Hg after dilatation. There was no pulmonary regurgitation murmur after the procedure. She was discharged from the hospital the next day. On day 15 after the procedure fever developed which responded to a course of antimalarial drugs. Two months later, breathlessness had improved to New York Heart Association class II and a repeat catheter study at this stage showed a peak systolic gradient of 84 mm Hg across the pulmonary valve. Repeat dilatation was not attempted. Two weeks after the second catheterisation an intermittent moderate grade fever developed. She complained of anorexia and weight loss. A loud pulmonary regurgitation murmur had developed. Echocardiography showed large mobile vegetations on both the pulmonary and tricuspid valves. Blood cultures for aerobic, anaerobic, and fungal organisms were negative. She was started on a combination of penicillin, cloxacillin, and gentamicin. The fever responded within a week and the antibiotic treatment was continued for six weeks. A repeat catheter study two months after treatment of infective endocarditis showed that the pressure drop across the pulmonary valve was further reduced to 23 mm Hg. The patient was reviewed several times in the past year and has remained well.

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Discussion

Infective endocarditis of the pulmonary valve as a complication of balloon dilatation has not been reported before. There is, however, a report of a case of aortic valve endocarditis after balloon dilatation in an immunocompromised patient.[2] Infective endocarditis is rare in patients with pulmonary stenosis. Johnson *et al* reported an incidence of 0·2 per 1000 patient-years.[3] However, studies in animals have clearly established that catheter induced endocardial damage can cause infective endocarditis when animals are bacteraemic.[4] Moreover, infective endocarditis of the pulmonary valve was common in a necropsy series of patients monitored with a Swan-Ganz catheter. These workers suggested that the infected vegetations were a direct consequence of catheter induced endocardial damage and subsequent bacteraemia.[5] Stretching and rupture of the valve tissue have been suggested as the mechanisms of the relief of obstruction by balloon dilatation of the pulmonary valve. These could make the valve vulnerable to endocarditis should bacteraemia occur. Our patient did not undergo dental or any other procedure after dilatation of the valve. Endocarditis in her case may have been related to the second cardiac catheterisation study, although bacteraemia seldom occurs during routine cardiac catheterisation.

Pulmonary valve vegetations have seldom been described on echocardiography. First, because pulmonary valve endocarditis is rare and secondly because it is often difficult to visualise the pulmonary valve on echocardiography.[6] Reports of multiple valve involvement with vegetations on the right side are still rare. The vegetations on the tricuspid valve in our patient could be the result of an extension of infection from the pulmonary valve. The late reduction in the pressure drop across the pulmonary valve after the second catheterisation was probably the result of "medical valvotomy" by infective endocarditis as has been reported before. Although we do not know the source of infection in the present case careful attention to sterile technique and prompt removal of intravenous lines may reduce the frequency of bacteraemia.

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VIEWS FROM THE PAST *Paul Rothschild*

Rothschild's promising German academic career was cut short when Hitler rose to power. He had spent two years in England as a postgraduate and with Lewis wrote papers on intermittent claudication and ischaemic paralysis of nerves. Lewis warned him of the Nazi danger looming; after he had returned to Frankfurt he received a telegram from Lewis offering him a base at University College Hospital and brought his family over. He subsequently entered general practice, also serving in the Royal Army Medical Corps. After his death in 1965 distinguished contemporaries including A V Hill and Sir George Pickering wrote in glowing terms of his abilities and distinction (Lewis collection).

DENNIS M KRIKLER

Br Heart J 1990;63:370–1

Management of an infected graft in the ascending aorta by an omental pedicel graft and irrigation with povidone iodine

William Joyce, Simon Huddy, E E John Smith

Abstract

An infected graft in the ascending aorta was managed by use of an omental pedicel graft and local irrigation with a dilute suspension of aqueous povidone iodine. This conservative approach is an alternative to the high risk procedure of graft replacement. The large abscess cavity associated with the aortic prosthesis was diagnosed by computed tomography.

Infection of an aortic prosthesis is a grave complication of cardiovascular surgery. Such infection is associated with a high mortality, limb loss, or both.[1] Usually the infected graft is removed and blood flow is rerouted through a clean field. This requires technically difficult surgery in very ill patients.

The omentum can wall off and localise potentially dangerous inflammation and gastrointestinal perforations. In most individuals the omentum, on a vascular pedicel, is large enough to be used in the thorax. This approach combined with the local antibacterial action of povidone iodine seemed an attractive alternative to replacement of an infected graft.

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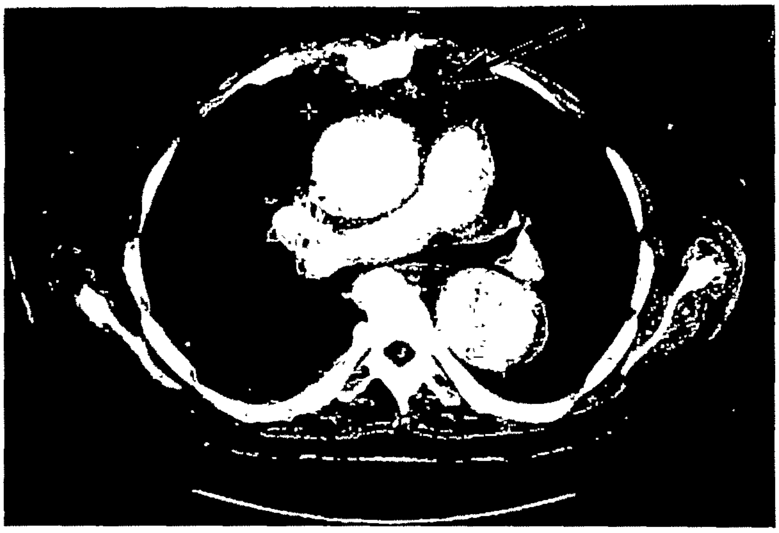
Case report

A 65 year old woman was referred with a 3 month history of increasing shortness of breath and a past history of rheumatic fever. On admission she was found to be in acute left ventricular failure and was initially treated medically. An echocardiogram showed considerable left ventricular dysfunction, severe aortic valve incompetence, and a 10 cm aneurysm of the aortic root. Subsequent cardiac catheterisation confirmed these findings.



Coronal computed tomogram at T5 level showing a large (8 cm diameter) periprosthetic abscess (+) and gas bubbles (arrow).

Four days after admission she deteriorated medically and required ventilation. After 48 hours of ventilation and an improvement in her condition she was taken to theatre. After initiation of cardiopulmonary bypass and cooling to 23°C centigrade, the aortic valve was replaced by a 21 mm Björk-Shiley valve. The aortic root aneurysm was resected and replaced with a 34 mm Gelseal graft.

At first she made a good postoperative recovery. But 3 weeks after operation a fever developed and the sternal wound began to discharge serous fluid. Two of six blood cultures grew a coagulase-negative staphylococcus while the sternal wound grew mixed coliform bacteria only. Treatment with intravenous pivampicillin and cefotaxime was started. Despite a normal white cell count the wound continued to discharge though it remained stable. Computed tomography showed a large abscess cavity associated with the aortic prosthesis. The vascular anastomosis seemed to be intact. She was therefore returned to theatre and the wound was re-explored.

A large periprosthetic abscess cavity was evacuated and the area was washed out thoroughly. The anastomosis was intact. The wound was extended into the upper abdomen. A flap (15 cm long) of greater omentum was mobilised off the transverse colon. This was delivered into the pericardial space through a substernal tunnel and was loosely held in place around the prosthesis. Three drains were inserted into the pericardial space. The wound was closed with sternal wires and deep tension sutures to superficial tissues.

The wound was irrigated postoperatively for 10 days with a dilute aqueous suspension of povidone iodine via the pericardial drains. Culture from the abscess cavity was sterile; none the less, a 6 week course of vancomycin was started. She made an otherwise uneventful postoperative recovery and she was well 18 months later.

Discussion

Infection of mediastinal aortic prostheses is uncommon but management remains a major surgical problem. Diagnosis can often be difficult. In our patient computed tomography established an early diagnosis that led to prompt surgical intervention.

Replacement of the infected graft is associated with a high risk. A more conservative approach by debridement and irrigation with povidone iodine reduces the local bacterial count but generally does not effect a cure.[2] The major contributing factor to failure in treatment of mediastinal graft infections is the obliteration of the dead space because of the rigidity of the retrosternal compartment.[3] An omental pedicel graft fills the dead space and reduces the potential for reinfection.[4-6]

As well as having anti-inflammatory properties, the omentum also contains an angiogenesis factor[7] which encourages new blood supply and provides fibroblasts to enhance healing. This in itself may be of considerable importance in the management of local sepsis. The omentum is large enough to be taken to anywhere in the body to treat graft sepsis.

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NOTICE

British Cardiac Society
The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May 1991.

Br Heart J 1990;63:372–3

Pseudoxanthoma elasticum presenting with myocardial infarction

Alistair K B Slade, Roy M John, R H Swanton

Abstract

A 31 year old man presented with an anterior myocardial infarction. He had a history of recurrent gastrointestinal bleeding of obscure cause since childhood and peripheral vascular disease. A clinical diagnosis of the type 1 dominant form of pseudoxanthoma elasticum was supported by histological data from skin biopsy.

Nearly all cases of myocardial infarction in middle aged men in the UK are caused by idiopathic atherosclerotic obstructive coronary artery disease. Premature coronary artery disease is frequently associated with hyperlipidaemia and diabetes mellitus but inherited abnormalities of connective tissue are a rare cause. We report a case of pseudoxanthoma elasticum presenting with a myocardial infarction.

Case report

A 31 year old white man presented to his general practitioner in January 1989 with a history of an unprovoked episode of prolonged anterior chest pain ten days before. An electrocardiogram showed changes of a recent anterior myocardial infarction. He was referred to hospital for outpatient assessment.

A past history of recurrent gastrointestinal bleeding and intermittent claudication of the right leg was elicited. Gastrointestinal bleeding had commenced at the age of 12 years with bouts of melaena requiring blood transfusions. Endoscopy of the upper gastrointestinal tract was normal and biopsy of an area of abnormal gastric mucosa showed only histological features consistent with gastric erosion. He continued to be troubled by repeated epigastric pains and melaena and was admitted to hospital several times for repeated investigations that failed to show a definite cause. Intermittent claudication affecting the right calf muscle appeared during the 12 months before his present episode and produced claudication pain at 600–800 yards (540–720 m). There was no family history of arterial disease, hypertension, or recurrent gastrointestinal bleeds. He smoked 30 cigarettes per day and alcohol intake was moderate.

There were no peripheral pulses below the femoral arteries on either side but there was no evidence of chronic ischaemia in the legs. He was normotensive (150/80 mm Hg). Retinal examination showed florid angioid streaks. He had small areas of pseudoxanthomatous skin on either side of his neck. The electrocardiogram confirmed changes of a Q wave anteroseptal myocardial infarction. Chest *x* ray showed mild cardiomegaly but no cardiac failure. Echocardiography showed an area of anteroapical hypokinesia without mural thrombus and fair overall left ventricular function. The lipid profile was normal. He was treated with 50 mg daily of atenolol and discharged with arrangements for an exercise test and clinic review. Six days later recurrence of chest pain led to admission to hospital. There was no objective evidence of new myocardial ischaemia or infarction. He was referred for urgent coronary angiography.

Cardiac catheterisation showed anteroapical left ventricular akinesia. The left anterior descending artery was occluded distal to the first septal branch (fig 1) and the distal vessel filled retrogradely from the right coronary artery which was dominant and normal. A small circumflex vessel was normal. The left ventricular ejection fraction was estimated to be 33% by radionuclide ventriculography.

The patient's cardiac symptoms settled with medical treatment and he was discharged on nitrates, diuretics, and captopril. Subsequent vascular surgical intervention by way of percutaneous angioplasty for a tight stenosis of the right common femoral artery was successful and greatly improved his claudication pain. Genetic counselling has been given.

Dicussion

Pseudoxanthoma elasticum is a rare inherited disorder of elastic tissue (incidence 1:160 000).[1] There are at least two dominant and two recessive inheritance patterns of the disease.[2] This patient has the type 1 dominant form with predominant vascular and eye changes.

Pseudoxanthoma elasticum is expressed clinically in three main areas: the skin, the eye, and the cardiovascular system. Widespread involvement of the muscular arteries also produces haemorrhagic symptoms in almost every organ system. The degree to which the various systems are affected is highly variable. Haemorrhage and cardiovascular complications usually bring patients to medical attention. The cardiovascular manifestations reported include peripheral vascular disease, coronary artery disease,

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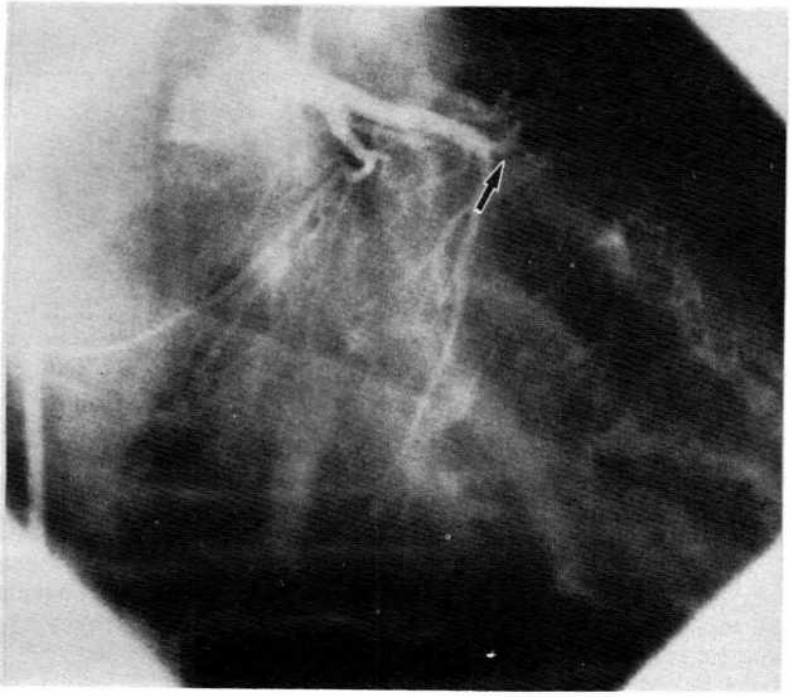

Figure 1 Left coronary angiogram in the right anterior oblique view showing occlusion of the left anterior descending artery distal to the first septal branch (arrow).

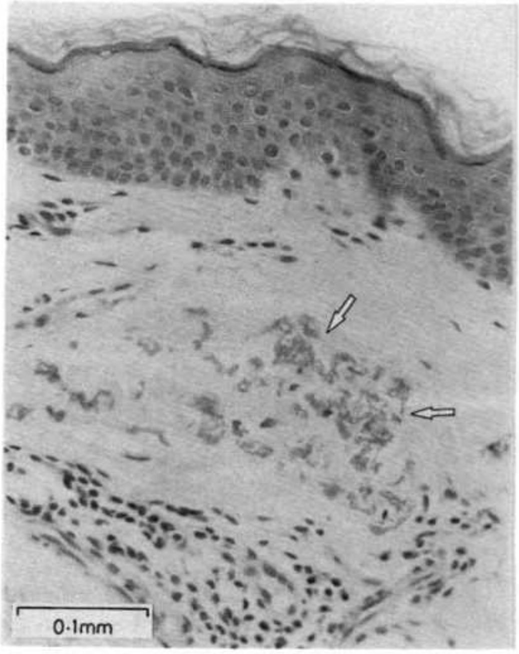

Figure 2 Histology of skin biopsy. Haematoxylin and eosin stain showing the swollen and clumped elastic fibres (arrows) in the dermis.

renovascular hypertension,[3] restrictive cardiomyopathy,[4] and an association with mitral valve prolapse.[5] The basic abnormality is not clear but is thought to involve degeneration of elastic tissue. Pathologically, disorganisation with fragmentation and clumping and calcification of elastic fibres in muscular arteries and endocardium has been noted in a necropsy study by Mendelsohn *et al*.[6] This study of three patients with pseudoxanthoma elasticum and congestive cardiac failure also showed considerable involvement of the atrial endocardium with extensive atrial calcification in one case.

Angina is well recognised and Carlborg *et al* reported angina pectoris in 15 of 29 patients with pseudoxanthoma elasticum at a mean age of 38 years.[7] However, myocardial infarction is thought to be rare. Coronary artery disease was reported in childhood[8] and coronary bypass grafting successfully undertaken in an 18 year old girl.[9]

Our patient had the classic features of pseudoxanthoma elasticum and histological examination of a skin biopsy specimen (fig 2) confirmed the diagnosis. The patient is suitable for coronary artery bypass grafting if angina becomes limiting. Retinal fluoroscopic angiography is necessary for identification of possible vessels liable to haemorrhage that require laser photocoagulation. Fortunately, there has been no recent recurrence of gastrointestinal haemorrhage but a bleed that is difficult to control could be treated by gastric arterial embolisation.[10]

In our patient there was a rare but important cause for coronary artery disease; young patients with a history of recurrent gastrointestinal bleeds presenting with vascular occlusive complications should be carefully examined for such rare inherited forms of connective tissue diseases.

We thank Dr T Matthews of Battle Hospital for help with the histological data.

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Br Heart J 1990;63:374

Obituary

BYRON EVANS

Byron Evans, a highly regarded and eminent Welsh general physician and cardiologist, died on 1 January 1990 at the age of 77. Born in Llanon, Cardiganshire, the only son of a master-mariner, he trained at the London Hospital, winning prizes in anatomy, pathology, and clinical medicine along the way. He qualified MB BS and in the Conjoint Board Examination in 1936, adding the London MD and MRCP three years later. His resident and other early appointments were all at the London and, in listing some of the major events in his life, he recalled that as a pathology assistant he had performed one thousand postmortems. During the second world war, he was officer in charge of a Royal Air Force medical division serving for some of the time in the Middle East. He then became a consultant in Cardiff, remaining until his retirement in 1977 as the senior physician in the University Hospital of Wales.

He was made Fellow of the Royal College of Physicians in 1957, was a member of the Association of Physicians of Great Britain and Ireland, and a member of the British Cardiac Society. His publications, reflecting a wide range of interests in general medicine and cardiology, included a chapter on communicable diseases in a textbook of medicine edited by Garland and Phillips and papers on leishmaniasis, toxic polyneuritis, the Fanconi syndrome, hyperparathyroidism, syphilitic aortitis, cardiomyopathy, aortic dissection, and various aspects of the treatment of hypertension and heart failure. He showed the advantage of oral thiazides over parenteral mercurials and in later publications confirmed the attributes of methyldopa.

He was one time chairman of the Society of Physicians in Wales, consultant to the Civil Service Sanatorium Society, member of the council and of the senate of the University Hospital of Wales, vice president of the Medical Protection Society, and member of the committee of management of the Medical Insurance Agency; from 1970 to 1974 he was a member of council of the British Cardiac Society. Awarded Her Majesty's Silver Jubilee Medal in 1977, in 1981 he was made LL D (Wales) in recognition of his distinguished contribution to medical education and the promotion of health.

He is remembered as an exceptionally able physician and a superb teacher of clinical method, gentle and caring in his dealings with patients and friendly, supportive, and loyal in his relationship with junior staff. As a first assistant at the London he had been inspired by Donald Hunter, William Evans, and Horace-Lord Evans and he often spoke of his indebtedness to them. They in turn regarded him with special affection. His tribute to William Evans, who survived in full vigour to the age of 92, appeared in the *British Heart Journal* in January 1989.

Enduring respect for Byron is evident especially from those who were his students in Cardiff. He took a close fatherly interest in the medical school rugby club, initiating the Provincial Hospitals Seven-a-side Tournament and donating the now much coveted Byron Evans cup. His sense of fun and expression of it with a stammer largely contrived—although in his student days it had been an embarrassment—are legendary. His hobbies included fishing on the Usk and the Teifi and sailing from Solva. He spoke Welsh fluently and true to his heritage had a great love of choral music. A compulsive conductor his style was unique, demanding, with uncharacteristic ferocity, hwyl before harmony and commitment before comprehension from choirs comprised usually of colleagues or disciples with opportunity if not cause for celebration. But those who may have concluded that the ease with which he emphasised the lighter aspects of life was one of his prime attributes would of course have been very wrong.

His illness before he died was protracted and sometimes distressing. Nursed expertly at home by his wife Kirsteen he showed courage, dignity, and unfailing humour. Greatly affected by the death of Pamela his first wife in 1973 he married Kirsteen in 1977 and had been blissfully happy in retirement. He is survived also by a son and twin daughters of his first marriage and by eight grandchildren.

EIRIAN WILLIAMS

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